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Research Article

Coexisting Conditions among Children and Adolescents with Cancer in a Section of the South African Private Health Sector: Perspectives from Drug Utilization Data

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ABSTRACT

Coexisting conditions are relatively common in children with cancer, however, there is a paucity of information on the prevalence of coexisting conditions in children with cancer in South Africa. This cross-sectional study aimed at investigating the common coexisting conditions occurring in children and adolescents younger than 19 years undergoing cancer chemotherapy in a section of the South African private health sector. Medicine claims data from 1 January 2008 to 31 December 2017 were queried to identify coexisting conditions using the International Classification of Diseases, Tenth Revision (ICD-10) codes indicated on reimbursed claims. Where ICD-10 codes per claim were non-specific, the pharmacological drug classes of non-cytotoxic medications claimed alongside these codes were categorized using the Monthly Index of Medical Specialties (MIMS) classification system and analyzed using the drug utilization 90% (DU90%) principle. Analysis of sub-pharmacologic drug classes was stratified according to gender and age groups. The reimbursement category of these medicines was noted. Data were analyzed descriptively. A total of 173 participants were included in the study. ICD-10 codes were available for 13.65% (*N* = 2631) of medicine claims. Diseases of the respiratory system (J00–J99, 7.15%), gastrointestinal tract (K00–K95, 1.60%), and skin disorders (L00–L99, 0.95%) were the most prevalent specific diagnoses identified. Non-specific ICD-10 codes were recorded on 86.35% (*n* = 2272) of non-cytotoxic medicine claims. The most frequently utilized pharmacological classes of medications included antimicrobial agents (17.40%), respiratory system agents (13.91%), and analgesics (10.64%). As determined from ICD-10 codes and medication claimed on reimbursed claims, children and adolescents being treated for cancers mostly suffered from acute conditions, in particular, microbial infections and diseases of the respiratory system. This indicates the need for the integration of antimicrobial surveillance programs into childhood and adolescent cancer care to curb antimicrobial infections.

1. INTRODUCTION

The resultant consequences of cancer, particularly immunosuppression, makes the presence of coexisting conditions—described as any medical condition that co-occurs with an index condition of interest in an individual—relatively common [1–3]. These conditions may arise from the malignancy itself or the treatment interventions used in the management of cancer [4,5]. For example, the immunosuppression associated with cancer predisposes children to conditions such as infections [6]. Children exposed to anthracyclines and cardiac irradiation are at risk of developing cardiotoxic complications such as valvular abnormalities and pericardial diseases during and after the treatment of cancer [7]. The use of high doses of alkylating agents and platinum compounds have also been identified as risk factors for lung fibrosis, pulmonary pneumonitis, thyroid abnormalities, ototoxicity, and impairment of renal function [8–11].

The risk of cancer, on the other hand, may be increased by the presence of other pre-existing conditions—especially those which are similarly associated with immunosuppression—such as Human Immunodeficiency Virus (HIV) infection [12]. HIV infection is a risk factor for some cancers including Kaposi sarcoma and non-Hodgkin's lymphoma [12] while hepatitis B virus infection has been linked to hepatocellular carcinoma [13]. Conditions that are characterized by chronic inflammation have also been found to stimulate tumorigenesis [14].

The prevalence of conditions coexisting in adults with cancer, especially chronic conditions such as hypertension, diabetes, peptic ulcer, and other cardiovascular conditions has been described in literature [15–18]. There is, however, a paucity of information on the prevalence of coexisting conditions in children with cancer in South Africa. Cognizance of coexisting conditions in patients with cancer is important due to their possible influence on treatment decisions—by the modification of treatment protocols—and the consequent impact on treatment outcome [1,15,19–21]. This study, therefore, aimed at identifying conditions that coexist with cancer in children and adolescents

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undergoing cancer chemotherapy in the South African private health sector.

2. MATERIALS AND METHODS

2.1. Study Design and Data Source

This study followed a descriptive cross-sectional design. Retrospective medicine claims data from 1 January 2008 to 31 December 2017, obtained from one of the largest South African PBM (Pharmaceutical Benefit Management) companies for medical aid schemes, were used for the analysis. This PBM company is currently responsible for the medical benefits of approximately 1.8 million beneficiaries (~20% of the total number of beneficiaries of medical aid schemes) enrolled in 47 (~62%) of medical schemes in South Africa.

Information on the database which was extracted and used in this study, included the date of birth (age), gender, the National Pharmaceutical Product Index (NAPPI) codes, prescription treatment dates, diagnoses [inferred from the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes], and the active substances (trade or generic name and pharmacological class) per reimbursed medicine item.

2.2. Study Population

The study population consisted of all children aged younger than 19 years with diagnostic codes for cancers (C00–C97) receiving treatment with cytotoxic medication reimbursed through patients' oncology benefits.

2.3. Measurements

Medicine claims data for the study population were queried to identify coexisting conditions, by identifying unique ICD-10 diagnostic codes recorded on claims for non-cytotoxic medicine items received during the period patients were on treatment for cancer.

Where ICD-10 diagnostic codes were missing or non-specific, we examined the non-cytotoxic medicine claimed during the period the patients were on treatment for cancer using the drug utilization 90% (DU90%) principle [22]. For this analysis, we categorized all non-cytotoxic medicine items claimed per patient into 22 main pharmacological groups based on the Monthly Index of Medical Specialties (MIMS) classification system [23] and removed all duplicates so that each unique medicine item was only counted once. These were then ranked in descending frequency to report the DU90% (i.e. the drug volume accounting for 90% of items claimed, categorized in main pharmacological drug class). Non-specific ICD-10 diagnostic codes refer to those that did not indicate a specific diagnosis and include repeat prescriptions (Z76), encountering health services in unspecified conditions (Z76.9), and failure of the patient or provider to disclose clinical information (U98.0 and U98.1, respectively).

Analysis of sub-pharmacological drug classes was stratified by gender and age, with age categorized into four age groups, namely 0–4 years, 5–9 years, 10–14 years, and 15 < 19 years, using the age at last birthday on the database as the reference date.

2.4. Statistical Analyses

The data were described using basic descriptive statistics such as frequencies, percentages, mean and standard deviation. Analyses of data were carried out using the SAS* program, version 9.4 [24].

2.5. Ethical Considerations

Ethical approval was obtained from the North-West University Health Research Ethics Committee (ethical approval number: NWU-00179-14-A1-08). Permission for the use of the database for this study was granted by the board of directors of the South African PBM company.

3. RESULTS

3.1. Demographic Characteristics of the Study Population

Table 1 summarizes the demographic characteristics of the study population. The study population consisted of a total of 173 patients, identified out of 209,390 patients younger than 19 years on the database from 2008 to 2017. The mean age of the study population was 10.05 ± 5.40 years. The majority were males (68.79%, $n = 119$), and in the 5–9 year age group (34.10%, $n = 59$). Patients aged 0–4 years comprised the smallest proportion of the study population at 15.61% ($n = 27$). Leukemias were the most prevalent cancers (39.88%, $n = 69$) followed by lymphomas (13.87%, $n = 24$).

Table 1 | Demographic characteristics of the study population

Characteristics	n (%)[a]
Overall population	173 (100)
Gender	
Male	119 (68.79)
Female	54 (31.21)
Age groups (years)	
0–4	27 (15.61)
5–9	59 (34.10)
10–14	40 (23.12)
15 < 19	47 (27.17)
Malignancy type	
Leukemias	69 (39.88)
Lymphomas	24 (13.87)
CNS neoplasms	19 (10.98)
Neuroblastoma	3 (1.73)
Retinoblastoma	6 (3.47)
Renal tumors	7 (4.05)
Hepatic tumors	1 (0.58)
Bone tumors	12 (6.94)
Soft tissue sarcomas	7 (4.05)
Germ cell tumors	6 (3.47)
Carcinoma and melanomas	17 (9.83)
Other and unspecified neoplasms	2 (1.16)

[a]Percentages calculated based on the total study population ($N = 173$).

3.2. Coexisting Conditions based on ICD-10 Codes

Table 2 depicts the number and type of coexisting conditions based on ICD-10 diagnostic codes recorded on reimbursed medicine claims. A total of 2631 medicine items were claimed for children and adolescents aged younger than 19 years on the database from 2008 to 2017. Specific diagnostic codes were only available for 13.65% ($n = 359$) of these medicine claims ($N = 2631$). Overall, 0.38% ($n = 10$) of medicine items claimed had diagnostic codes for chronic conditions; these included asthma (J45.9, 0.11%, $n = 3$), essential hypertension (I10, 0.04%, $n = 1$), major depressive disorders (F32.2 and F32.3, 0.15%, $n = 4$), anxiety disorders (F41.9, 0.04%, $n = 1$) and epilepsy (G40.2, 0.04%, $n = 1$).

The most prevalent acute coexisting conditions identified in the study population included diseases of the respiratory system (J00–J99, 7.15%, $N = 188$), in particular acute tonsillitis (J03.9, 17.55%, $n = 33$) and bronchitis (J20.9, 10.11%, $n = 19$), and diseases of the Gastrointestinal Tract (GIT) (K00–K95, 1.60%, $N = 42$), particularly non-infective gastroenteritis (K52.9, 19.05%, $n = 8$) and gastric ulcer (K25.9, 14.29%, $n = 6$). Others included skin disorders (L00–L99, 0.95%, $N = 25$), particularly dermatitis (L30.9, 24.00%, $n = 6$) and impetigo (L01.0, 16.00%, $n = 4$), and disorders of the musculoskeletal system (M00–M99, 0.91%, $N = 24$), particularly osteomyelitis (M86.25, 16.70%, $n = 4$).

3.3. Coexisting Conditions based on Non-specific ICD-10 Codes

The majority of medicine items, representing 86.35% ($n = 2272$) of the total non-cytotoxic medicine items utilized by the study

Table 2 | Coexisting conditions based on ICD-10 diagnostic codes associated with medicine claims

Conditions based on ICD-10 codes	Number of medicine items associated with ICD-10 codes, n (%)[a]
Total medicine items claimed, N	2631
Conditions with specified diagnostic codes	359 (13.65)
Diseases of the respiratory system	188 (7.15)
Diseases of the gastrointestinal tract	42 (1.60)
Skin disorders	25 (0.95)
Disorders of the musculoskeletal system	24 (0.91)
Pain	17 (0.65)
Genitourinary system disorders	15 (0.57)
Diseases of the ear	13 (0.49)
Infectious diseases	9 (0.34)
Fever of unknown origin	6 (0.23)
Behavioral and mental disorders	5 (0.19)
Central nervous system disorders	3 (0.11)
Ascites	3 (0.11)
Anemia	2 (0.08)
Ocular diseases	2 (0.08)
Diseases of the circulatory system	2 (0.08)
Immunizations against infectious diseases	2 (0.08)
Hepatic abnormalities	1 (0.04)
Conditions with non-specified diagnostic code[b]	2272 (86.35)

[a]Percentages calculated based on the total number of medicine items claimed during the study period ($N = 2631$). [b]These include diagnostic codes for repeat prescriptions (Z76.0), failure for patient or clinician to disclose clinical information (U98.0 and U98.1), encountering health services in unspecified conditions and missing codes (Z76.9).

population, were claimed under non-specific diagnostic codes. Table 3 depicts the DU90% of medicine claims with non-specific diagnostic codes over the study period. The main pharmacological classes constituting the DU90% included antimicrobials (17.47%, $n = 397$), respiratory system agents (13.25%, $n = 301$), analgesics (10.26%, $n = 233$), Ear, Nose and Throat (ENT) agents (9.73%, $n = 221$), GIT agents (7.75%, $n = 176$) and Central Nervous System (CNS) agents (6.65%, $n = 151$). Others included autacoids (6.34%, $n = 144$), dermatologicals, (4.97%, $n = 113$), endocrine agents (4.84%, $n = 110$), herbal preparations (3.57%, $n = 81$), musculoskeletal agents (3.26%, $n = 74$) and anesthetics (2.82%, $n = 64$) (Table 3).

Tables 4 and 5 depict the breakdown of the sub-pharmacological classes of all medications ($N = 2631$) claimed at least once by the study population during the study period, by gender and age group. Antimicrobial agents were the most prevalent pharmacological group of medicines (17.41%, $n = 458$), followed by respiratory system agents (13.91%, $n = 366$), analgesics (10.64%, $n = 280$), ENT agents (9.65%, $n = 254$), GIT agents (7.49%, $n = 197$), CNS agents (6.46%, $n = 170$), autacoids (6.31%, $n = 166$) and dermatologicals (5.32%, $n = 140$). Special foods were the least claimed agents (0.11%, $n = 3$).

Beta-lactam antimicrobials were the most prevalent antimicrobial agents ($N = 458$) accounting for 49.12% ($n = 225$) of claims. This was followed by sulphonamides and sulphonamide-containing combinations (14.19%, $n = 65$), and erythromycin and other macrolides (10.70%, $n = 49$). Medicines for the treatment of coughs and colds (63.93%, $n = 234$) were the most prevalent class of medications among respiratory system agents ($N = 366$), followed by bronchodilators (21.58%, $n = 79$) and mucolytics (8.47%, $n = 31$). Analgesic combination products (56.79%, $n = 159$) were the most frequently received analgesics ($N = 280$), followed by analgesics and antipyretics (35.71%, $n = 100$) (Table 4).

Analysis by gender shows that the majority of medications (64.88%, $n = 1707$) were claimed for males. Antimicrobials (11.71% and 5.70%), respiratory system agents (9.39% and 4.52%), and analgesics (6.80% and 3.84%) were the three most prevalent pharmacological classes received in males and females, respectively (Table 4). Beta-lactams, medicines for coughs and colds, and combination analgesics were the most prevalent sub-pharmacological classes in

Table 3 | Pharmacological classes within DU 90% of medicines claimed under non-specific diagnostic codes

Pharmacological class	n (%)[a]
Antimicrobials	397 (17.47)
Respiratory agents	301 (13.25)
Analgesics	233 (10.26)
Ear, nose and throat agents	221 (9.73)
Gastrointestinal tract agents	176 (7.75)
Central nervous system agents	151 (6.65)
Autacoids	144 (6.34)
Dermatologicals	113 (4.97)
Endocrine agents	110 (4.84)
Herbal preparations	81 (3.57)
Musculoskeletal agents	74 (3.26)
Anesthetics	64 (2.82)

[a]Percentages calculated based on the total number of medicine items claimed under non-specific diagnostic codes ($N = 2272$).

Table 4 Pharmacological classes of non-cytotoxic medications used in children and adolescents with cancer in the overall study population and by gender groups according to the Monthly Index of Medical Specialties classification

Prevalence of main pharmacological classes in the overall study population and gender groups				Prevalence of sub-pharmacological classes in the overall study population and gender groups			
Main pharmacological classification	Overall prevalence, n (%)	Prevalence in males, n (%)	Prevalence in females, n (%)	Sub-pharmacological classification	Overall prevalence, n (%)	Prevalence in males, n (%)	Prevalence in females, n (%)
Antimicrobials	458 (17.40)	308 (11.71)	150 (5.70)	Beta-lactams	225 (8.55)	156 (5.93)	69 (2.62)
				Sulphonamides and combinations	65 (2.47)	44 (1.67)	21 (0.80)
				Erythromycin and other macrolides	49 (1.86)	35 (1.33)	14 (0.53)
				Anti-fungal agents	46 (1.75)	27 (1.03)	19 (0.72)
				Anti-viral agents	25 (0.95)	17 (0.65)	8 (0.30)
				Quinolones	24 (0.91)	15 (0.57)	9 (0.34)
				Anti-protozoal agents	13 (0.49)	6 (0.23)	7 (0.27)
				Tetracyclines	5 (0.19)	4 (0.15)	1 (0.04)
				Others	6 (0.23)	4 (0.15)	2 (0.08)
Respiratory system agents	366 (13.91)	247 (9.39)	119 (4.52)	Coughs and colds	234 (8.89)	154 (5.85)	80 (3.04)
				Bronchodilators	79 (3.00)	53 (2.01)	26 (0.99)
				Mucolytics	31 (1.18)	22 (0.84)	9 (0.34)
				Anti-asthmatics	22 (0.84)	18 (0.68)	4 (0.15)
Analgesics	280 (10.64)	179 (6.80)	101 (3.84)	Combination products	159 (6.04)	95 (3.61)	64 (2.43)
				Analgesics and antipyretics	100 (3.80)	67 (2.55)	33 (1.25)
				Narcotic analgesics	14 (0.53)	11 (0.42)	3 (0.11)
				Other agents	7 (0.27)	6 (0.23)	1 (0.04)
Ear, nose and throat agents	254 (9.65)	163 (6.20)	91 (3.46)	Topical nasal preparations	156 (5.93)	106 (4.03)	50 (1.90)
				Mouth and throat preparations	79 (3.00)	41 (1.56)	38 (1.44)
				Ear drops and ointments	19 (0.72)	16 (0.61)	3 (0.11)
Gastrointestinal Tract (GIT) agents	197 (7.49)	132 (5.02)	65 (2.47)	Acid reducers	91 (3.46)	62 (2.36)	29 (1.10)
				Antispasmodics	32 (1.22)	22 (0.84)	10 (0.38)
				Laxatives	30 (1.14)	19 (0.72)	11 (0.42)
				Antidiarrhoeals	23 (0.87)	16 (0.61)	7 (0.27)
				Other GIT agents	13 (0.49)	9 (0.34)	4 (0.15)
				Suppositories and anal ointments	8 (0.30)	4 (0.15)	4 (0.15)
Central Nervous System (CNS) agents	170 (6.46)	106 (4.03)	64 (2.43)	Anti-vertigo and antiemetics	54 (2.05)	29 (1.10)	25 (0.95)
				Anti-epileptics	34 (1.29)	25 (0.95)	9 (0.34)
				Antidepressants	29 (1.10)	18 (0.68)	11 (0.42)
				Sedative hypnotics	24 (0.91)	15 (0.57)	9 (0.34)
				Anxiolytics	16 (0.61)	11 (0.42)	5 (0.19)
				Antipsychotics	6 (0.23)	3 (0.11)	3 (0.11)
				CNS stimulants	4 (0.15)	3 (0.11)	1 (0.04)
				Anti-Parkinson agents	2 (0.08)	2 (0.08)	0 (0.0)
				Anti-migraine agents	1 (0.04)	0 (0.0)	1 (0.04)
Autacoids	166 (6.31)	112 (4.26)	54 (2.05)	Antihistamines	112 (4.26)	71 (2.70)	41 (1.56)
				Serotonin antagonists	50 (1.90)	38 (1.44)	12 (0.46)
				NK1 antagonists	4 (0.15)	3 (0.11)	1 (0.04)
Dermatologicals	140 (5.32)	80 (3.04)	60 (2.28)	Corticosteroids	49 (1.86)	30 (1.14)	19 (0.72)
				Fungicides	27 (1.03)	16 (0.61)	11 (0.42)
				Anti-bacterial antiseptic agents	24 (0.91)	15 (0.57)	9 (0.34)
				Other dermatologicals	16 (0.61)	9 (0.34)	7 (0.27)
				Emollients and protectives	12 (0.46)	5 (0.19)	7 (0.27)
				Acne preparations	11 (0.42)	5 (0.19)	6 (0.23)
				Psoriasis	1 (0.04)	0 (0.0)	1 (0.04)

Main class				Sub-class			
Endocrine system agents	122 (4.64)	85 (3.23)	37 (1.41)	Corticosteroids	116 (4.41)	81 (3.08)	35 (1.33)
				Antidiabetic agents	4 (0.15)	4 (0.15)	0 (0.0)
				Sex hormones	2 (0.08)	0 (0.0)	2 (0.08)
Musculoskeletal agents	91 (3.45)	52 (1.98)	39 (1.48)	Non-steroidal anti-inflammatory agents	70 (2.66)	42 (1.60)	28 (1.06)
				Topical agents	10 (0.38)	7 (0.27)	3 (0.11)
				Anti-gout agents	9 (0.34)	3 (0.11)	6 (0.23)
				Centrally acting muscle relaxants	2 (0.08)	0 (0.0)	2 (0.08)
Herbal preparations	85 (3.23)	61 (2.32)	24 (0.91)	Natural products	85 (3.23)	61 (2.32)	24 (0.91)
Anesthetics	72 (2.74)	43 (1.63)	29 (1.10)	Local anesthetics	41 (1.56)	21 (0.80)	20 (0.76)
				General anesthetics	30 (1.14)	22 (0.84)	8 (0.30)
				Muscle relaxants	1 (0.04)	0 (0.0)	1 (0.04)
Vitamins, tonics, minerals and electrolytes	59 (2.24)	39 (1.48)	20 (0.76)	Minerals and electrolytes	44 (1.67)	28 (1.06)	16 (0.61)
				Vitamins	13 (0.49)	9 (0.34)	4 (0.15)
				Vitamins with minerals	1 (0.04)	1 (0.04)	0 (0.00)
				Tonics	1 (0.04)	1 (0.04)	0 (0.00)
Ophthalmics	37 (1.41)	25 (0.95)	12 (0.46)	Anti-infectives	16 (0.61)	14 (0.53)	2 (0.08)
				Anti-infective and corticoid combinations	12 (0.46)	6 (0.23)	6 (0.23)
				Corticoids	3 (0.11)	2 (0.08)	1 (0.04)
				Decongestants	3 (0.11)	2 (0.08)	1 (0.04)
				Others	2 (0.08)	1 (0.04)	1 (0.04)
				Glaucoma	1 (0.04)	0 (0.0)	1 (0.04)
Urinary system agents	30 (1.14)	16 (0.61)	14 (0.53)	Diuretics	10 (0.38)	5 (0.19)	5 (0.19)
				Urinary alkalinizers	6 (0.23)	1 (0.04)	5 (0.19)
				Urinary antiseptics	1 (0.04)	0 (0.0)	1 (0.04)
				Others	13 (0.49)	10 (0.38)	3 (0.11)
Biologicals	29 (1.10)	17 (0.65)	12 (0.46)	Biologicals	29 (1.10)	17 (0.65)	12 (0.46)
Blood and hematopoetic agents	23 (0.87)	14 (0.53)	9 (0.34)	Anticoagulants	15 (0.57)	9 (0.34)	6 (0.23)
				Hematinics	5 (0.19)	4 (0.15)	1 (0.04)
				Hemostatics	3 (0.11)	1 (0.04)	2 (0.08)
Anthelmintics	18 (0.68)	9 (0.34)	9 (0.34)	Anthelmintics	18 (0.68)	9 (0.34)	9 (0.34)
Cardiovascular agents	15 (0.57)	13 (0.49)	2 (0.08)	Antihypertensive agents	7 (0.27)	7 (0.27)	0 (0.0)
				Anti-arrythmics	4 (0.15)	3 (0.11)	1 (0.04)
				Anti-anginal agents	1 (0.04)	0 (0.00)	1 (0.04)
				Other vasodilators	1 (0.04)	1 (0.04)	0 (0.00)
				Vasoconstrictors	1 (0.04)	1 (0.04)	0 (0.00)
				Hipolipidemic agents	1 (0.04)	1 (0.04)	0 (0.00)
Genital system	9 (0.34)	0 (0.0)	9 (0.34)	Contraceptives	8 (0.30)	0 (0.00)	8 (0.30)
				Vaginal preparations	1 (0.04)	0 (0.00)	1 (0.04)
Autonomic agents	7 (0.27)	5 (0.19)	2 (0.08)	Anticholinergics	4 (0.15)	3 (0.11)	1 (0.04)
				Sympathomimetics	2 (0.08)	2 (0.08)	0 (0.00)
				Cholinergics	1 (0.04)	0 (0.00)	1 (0.04)
Special foods	3 (0.11)	1 (0.04)	2 (0.08)	Special foods	3 (0.11)	1 (0.04)	2 (0.08)
Total main class	2361 (100.00)	1707 (64.88)	924 (35.12)	Total sub-class	2361 (100.00)	1707 (64.88)	924 (35.12)

Table 5 | Distribution of the pharmacological classes of non-cytotoxic medications used in children and adolescents with cancer, by age group, according to the Monthly Index of Medical Specialties classification

Prevalence of pharmacological classes in age groups					Prevalence of sub-pharmacological classes in age group				
Main pharmacological classification	Prevalence in 0–4 years, *n* (%)	Prevalence in 5–9 years, *n* (%)	Prevalence in 10–14 years, *n* (%)	Prevalence in 15 < 19 years, *n* (%)	Sub-pharmacological group	Prevalence in 0–4 years, *n* (%)	Prevalence in 5–9 years, *n* (%)	Prevalence in 10–14 years, *n* (%)	Prevalence in 15 < 19 years, *n* (%)
Antimicrobials	61 (2.32)	225 (8.55)	62 (2.36)	110 (4.18)	Beta-lactams	43 (1.63)	113 (4.29)	31 (1.18)	38 (1.44)
					Sulphonamides and combinations	7 (0.27)	41 (1.56)	8 (0.30)	9 (0.34)
					Erythromycin and other macrolides	7 (0.27)	27 (1.03)	6 (0.23)	9 (0.34)
					Anti-fungal agents	2 (0.08)	18 (0.68)	8 (0.30)	18 (0.68)
					Anti-viral agents	1 (0.04)	17 (0.65)	1 (0.04)	6 (0.23)
					Quinolones	0 (0.00)	2 (0.08)	4 (0.15)	18 (0.68)
					Anti-protozoal agents	1 (0.04)	6 (0.23)	0 (0.00)	6 (0.23)
					Tetracyclines	0 (0.00)	0 (0.00)	2 (0.08)	3 (0.11)
					Others	0 (0.00)	1 (0.04)	2 (0.08)	3 (0.11)
Respiratory system agents	48 (1.82)	167 (6.35)	58 (2.2)	93 (3.53)	Coughs and colds	28 (1.06)	89 (3.38)	43 (1.63)	74 (2.81)
					Bronchodilators	13 (0.49)	43 (1.63)	10 (0.38)	13 (0.49)
					Mucolytics	3 (0.11)	20 (0.76)	3 (0.11)	5 (0.19)
					Anti-asthmatics	4 (0.15)	15 (0.57)	2 (0.08)	1 (0.04)
Analgesics	41 (1.56)	106 (4.03)	50 (1.90)	83 (3.15)	Combination products	16 (0.61)	46 (1.75)	32 (1.22)	65 (2.47)
					Analgesics and antipyretics	25 (0.95)	53 (2.01)	14 (0.53)	8 (0.30)
					Narcotic analgesics	0 (0.00)	7 (0.27)	2 (0.08)	5 (0.19)
					Other agents	0 (0.00)	0 (0.00)	2 (0.08)	5 (0.19)
Ear, nose and throat agents	24 (0.91)	103 (3.91)	53 (2.01)	74 (2.81)	Topical nasal preparations	20 (0.76)	63 (2.39)	32 (1.22)	41 (1.56)
					Mouth and throat preparations	2 (0.08)	33 (1.25)	17 (0.65)	27 (1.03)
					Ear drops and ointments	2 (0.08)	7 (0.27)	4 (0.15)	6 (0.23)
Gastrointestinal Tract (GIT) agents	20 (0.76)	57 (2.17)	55 (2.09)	65 (2.47)	Acid reducers	7 (0.27)	17 (0.65)	26 (0.99)	41 (1.56)
					Antispasmodics	5 (0.19)	11 (0.42)	9 (0.34)	7 (0.27)
					Laxatives	3 (0.11)	14 (0.53)	7 (0.27)	6 (0.23)
					Antidiarrheals	3 (0.11)	7 (0.27)	6 (0.23)	7 (0.27)
					Other GIT agents	2 (0.08)	4 (0.15)	5 (0.19)	2 (0.08)
					Suppositories and anal ointments	0 (0.00)	4 (0.15)	2 (0.08)	2 (0.08)
Central Nervous System (CNS) agents	12 (0.46)	35 (1.33)	37 (1.41)	86 (3.27)	Anti-vertigo and antiemetics	4 (0.15)	14 (0.53)	11 (0.42)	25 (0.95)
					Anti-epileptics	6 (0.23)	12 (0.46)	7 (0.27)	9 (0.34)
					Antidepressants	0 (0.00)	2 (0.08)	10 (0.38)	17 (0.65)
					Sedative hypnotics	0 (0.00)	2 (0.08)	2 (0.08)	20 (0.76)
					Anxiolytics	1 (0.04)	3 (0.11)	3 (0.11)	9 (0.34)
					Antipsychotics	0 (0.00)	1 (0.04)	2 (0.08)	3 (0.11)
					CNS stimulants	1 (0.04)	1 (0.04)	0 (0.00)	2 (0.08)
					Anti-Parkinson agents	0 (0.00)	0 (0.00)	2 (0.08)	0 (0.00)
					Anti-migraine agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Autacoids	24 (0.91)	75 (2.85)	31 (1.18)	36 (1.37)	Antihistamines	18 (0.68)	53 (2.01)	15 (0.57)	26 (0.99)
					Serotonin antagonists	6 (0.23)	22 (0.84)	15 (0.57)	7 (0.27)
					NK1 antagonists	0 (0.00)	0 (0.00)	1 (0.04)	3 (0.11)
Dermatologicals	17 (0.65)	44 (1.67)	28 (1.06)	51 (1.94)	Corticosteroids	8 (0.30)	18 (0.68)	9 (0.34)	14 (0.53)
					Fungicides	5 (0.19)	12 (0.46)	6 (0.23)	4 (0.15)
					Anti-bacterial antiseptic agents	2 (0.08)	9 (0.34)	4 (0.15)	9 (0.34)
					Other dermatologicals	2 (0.08)	3 (0.11)	4 (0.15)	7 (0.27)
					Emollients and protectives	0 (0.00)	2 (0.08)	4 (0.15)	6 (0.23)
					Acne preparations	0 (0.00)	0 (0.00)	1 (0.04)	10 (0.38)
					Psoriasis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)

Main group					Sub-group				
Endocrine system agents	14 (0.53)	54 (2.05)	21 (0.80)	33 (1.25)	Corticosteroids	14 (0.53)	54 (2.05)	21 (0.80)	27 (1.03)
					Antidiabetic agents	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.15)
					Sex hormones	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.08)
Musculoskeletal agents	10 (0.38)	25 (0.95)	15 (0.57)	41 (1.56)	Non-Steroidal anti-inflammatory agents	7 (0.27)	22 (0.84)	9 (0.34)	32 (1.22)
					Topical agents	0 (0.00)	2 (0.08)	3 (0.11)	5 (0.19)
					Anti-gout agents	3 (0.11)	1 (0.04)	2 (0.08)	3 (0.11)
					Centrally acting muscle relaxants	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.04)
Herbal preparations	19 (0.72)	37 (1.41)	9 (0.34)	20 (0.76)	Natural products	19 (0.72)	37 (1.41)	9 (0.34)	20 (0.76)
Anesthetics	21 (0.80)	15 (0.57)	18 (0.68)	18 (0.68)	Local anesthetics	8 (0.30)	10 (0.38)	8 (0.30)	15 (0.57)
					General anesthetics	12 (0.46)	5 (0.19)	10 (0.38)	3 (0.11)
					Muscle relaxants	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Vitamins, tonics, minerals and electrolytes	10 (0.38)	20 (0.76)	15 (0.57)	14 (0.53)	Minerals and electrolytes	9 (0.34)	15 (0.57)	10 (0.38)	10 (0.38)
					Vitamins	0 (0.00)	5 (0.19)	4 (0.15)	4 (0.15)
					Vitamins with minerals	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)
					Tonics	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Ophthalmics	10 (0.38)	15 (0.57)	4 (0.15)	8 (0.30)	Anti-infectives	7 (0.27)	8 (0.30)	0 (0.00)	1 (0.04)
					Anti-infective and corticoid combinations	3 (0.11)	4 (0.15)	2 (0.08)	3 (0.11)
					Corticoids	0 (0.00)	1 (0.04)	1 (0.04)	1 (0.04)
					Decongestants	0 (0.00)	0 (0.00)	1 (0.04)	2 (0.08)
					Others	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.04)
					Glaucoma	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Urinary system agents	2 (0.08)	8 (0.30)	3 (0.11)	17 (0.65)	Diuretics	0 (0.00)	2 (0.08)	0 (0.00)	8 (0.30)
					Urinary alkalinizers	1 (0.04)	0 (0.00)	0 (0.00)	5 (0.19)
					Urinary antiseptics	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Others	1 (0.04)	6 (0.23)	3 (0.11)	3 (0.11)
Biologicals	9 (0.34)	7 (0.27)	2 (0.08)	11 (0.42)	Biologicals	9 (0.34)	7 (0.27)	2 (0.08)	11 (0.42)
Blood and hematopoetic agents	2 (0.08)	4 (0.15)	3 (0.11)	14 (0.53)	Anticoagulants	2 (0.08)	3 (0.11)	2 (0.08)	8 (0.30)
					Hematinics	0 (0.00)	1 (0.04)	1 (0.04)	3 (0.11)
					Hemostatics	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.11)
Anthelmintics	3 (0.11)	11 (0.42)	4 (0.15)	0 (0.00)	Anthelmintics	3 (0.11)	11 (0.42)	4 (0.15)	0 (0.00)
Cardiovascular agents	2 (0.08)	5 (0.19)	0 (0.00)	8 (0.30)	Antihypertensive agents	1 (0.04)	3 (0.11)	0 (0.00)	3 (0.11)
					Anti-arrythmics	1 (0.04)	2 (0.08)	0 (0.00)	1 (0.04)
					Anti-anginal agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Other vasodilators	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Vasoconstrictors	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Hipolipidemic agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Genital system	0 (0.00)	0 (0.00)	1 (0.04)	8 (0.30)	Contraceptives	0 (0.00)	0 (0.00)	0 (0.00)	8 (0.30)
					Vaginal preparations	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)
Autonomic agents	4 (0.15)	0 (0.00)	3 (0.11)	0 (0.00)	Anticholinergics	2 (0.08)	0 (0.00)	2 (0.08)	2 (0.08)
					Sympathomimetics	1 (0.04)	0 (0.00)	1 (0.04)	1 (0.04)
					Cholinergics	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Special foods	0 (0.00)	0 (0.00)	2 (0.08)	1 (0.04)	Special foods	0 (0.00)	0 (0.00)	2 (0.08)	1 (0.04)
Total main groups	353 (13.42)	1013 (38.50)	474 (18.02)	791 (30.06)	Total sub-groups	353 (13.42)	1013 (38.50)	474 (18.02)	791 (30.06)

the antimicrobial, respiratory system agents, and analgesic classes, respectively in both gender groups.

For the age groups, the highest proportion of medicine items (38.50%, $n = 1\,013$) was claimed for the 5–9 years age group over the study period (Table 5). This was followed by the 15 < 19 years age group (30.06%, $n = 791$), and the 10–14 years age group (18.02%, $n = 474$). The smallest proportion of medications (13.42%, $n = 353$) was claimed for the 0–4 years age group. Beta-lactams, medicines for colds and coughs, and combination analgesics were the most frequently received antimicrobial, respiratory system agents, and analgesics, respectively, across all age groups (Table 5).

Table 6 illustrates the reimbursement categories from which medicine claims of patients were paid. A total of 2160 medicine items, representing 82.10% of the total medicines utilized by the patient population in this study, were reimbursed from the patients' acute benefits. This was followed by medicines classified as over-the-counter medications (9.84%, $n = 259$). Medicines classified as chronic medications were the least claimed class of medicines, accounting for 0.49% ($n = 13$) of the medicine items claimed during the study period. This trend was observed across all gender and age groups except for the 10–14 years age group in which Prescribed Minimum Benefits (PMB) was the category with the fewest reimbursements (Table 6).

4. DISCUSSION

This study aimed at identifying coexisting conditions in children and adolescents on treatment for cancer using the ICD-10 codes recorded on claims for non-cytotoxic medicines. In the absence of specific ICD-10 codes, the main pharmacological classes claimed were analyzed. The results of this study indicate that specific ICD-10 codes were available for only 13.65% ($N = 2631$) of the total medicine claims over the study period. Non-specific ICD-10 codes indicated on the majority of medicine claims included those for repeat prescriptions (Z76.0), encountering health services in unspecified conditions (Z76.9), and failure of patient or provider to disclose clinical information (U98.0 and U98.1). ICD-10 codes, developed by the World Health Organization, are standard codes used to describe medical and health information and were introduced in the South African private health sector in 2005 [25]. Medical schemes utilize these standard codes for easy identification of diagnoses, especially those classified as PMBs and chronic, and appropriate reimbursements. The absence of or use of non-specific

ICD-10 codes limits the ability to identify important patient health information to support public health research and reporting [26]. There may, therefore, be an underestimation of the prevalence of coexisting conditions in our study.

Secondly, our results showed that the majority (97.21%) of medicine items reimbursed with specific ICD-10 codes were indicated for acute conditions while only about 3% were for chronic conditions. This is supported by the higher proportion (82.10%) of all medicine claims reimbursed from patients' acute benefits. This is to be expected because increasing age is a very important non-modifiable risk factor for chronic conditions [27,28]. Children are, therefore, less likely to develop chronic conditions. However, taking into account the potential complications of cancer and its treatment, chronic conditions may be identified in children on antineoplastic therapy. Chronic conditions identified in our study included hypertension which could be a result of the nephrotoxicity associated with the use of some chemotherapeutic agents such as cisplatin and ifosfamide [29]. Corticosteroids, which are mostly used as an adjunct therapy for some childhood cancers, have also been associated with hypertension in these patients [30]. Major Depressive Disorders (MDDs) and anxiety were also identified in our patient population and this could be attributed to psychological stress associated with cancer diagnosis and treatment [31]. Depression resulting from psychological stress is more prevalent in older children and adolescents with cancer due to the concurrence of the disease and their developmental stage [32]. This was confirmed in a study by Akimana et al. [33] which established that patients aged 10–17 years were four times more likely to be diagnosed with MDDs in comparison to younger children. This high prevalence of depression in older children and adolescents is confirmed by the prevalent use of antidepressants in the 10–14 and 15 < 19 years age group, compared to the other age groups in our study population.

Other chronic conditions identified in the study included epilepsy and asthma. The coexistence of epilepsy and cancer in our study is supported by the relatively high use of antiepileptic drugs as observed from our analysis based on the main pharmacological classes of all medicine claims. Epilepsy, which is mostly characterized by seizures, may be drug-induced, result from metastasis of primary brain tumor, or may be a complication of leukemia with brain involvement [34,35]. Epilepsy has been indicated as the most common chronic neurological condition in children [36] with a prevalence of 0.7% reported in rural South African children [37]. Some studies in South Africa have demonstrated a 9–34% prevalence of asthma in children in the general population, with a

Table 6 | Classification of medicine items according to reimbursement category

	Acute	Chronic	OTC[a]	PMB[b]	Other	Total	*p*-value
Total population, *n* (%)[c]	2160 (82.10)	13 (0.49)	259 (9.84)	32 (1.22)	167 (6.35)	2631	
Gender, *n* (%)[c]							
Male	1366 (51.92)	2 (0.08)	184 (7.00)	20 (0.76)	135 (5.13)	1707 (64.88)	<0.0001
Female	794 (30.18)	11 (0.42)	75 (2.85)	12 (0.46)	32 (1.22)	924 (35.12)	
Age groups, *n* (%)[c]							
0–4 years	312 (11.86)	0 (0.00)	29 (1.10)	0 (0.00)	12 (0.46)	353 (13.42)	<0.0001
5–9 years	804 (30.56)	0 (0.00)	102 (3.88)	19 (0.72)	88 (3.34)	1013 (38.50)	
10–14 years	388 (14.75)	7 (0.27)	60 (2.28)	1 (0.04)	18 (0.68)	474 (18.02)	
15 < 19 years	656 (24.93)	6 (0.23)	68 (2.58)	12 (0.46)	49 (1.86)	791 (30.06)	

[a]OTC, Over-the-counter; [b]PMB, Prescribed minimum benefits; [c]Percentages calculated using the total number of medicine items utilized ($N = 2631$).

higher rate in residents of urban communities [38,39]. This confirms asthma as one of the prevalent chronic diseases in children. Asthma as a coexisting condition in our study population is supported by the prevalent use of anti-asthmatics, bronchodilators, antihistamines and corticosteroids. This is in contrast with previous studies that established a possible reduction in the prevalence of asthma symptoms and the need for asthma preventive therapies in children receiving chemotherapeutic agents [40,41]. It should, however, be noted that data for this study were expressed descriptively because of low numbers, and comparison with the prevalent use of asthma preventive therapy in patients unexposed to chemotherapeutic agents was outside the scope of this study.

Thirdly, diseases of the respiratory system were the most prevalent acute conditions overall, followed by diseases of the GIT, disorders of the skin, and diseases of the musculoskeletal system. Acute tonsillitis, acute upper respiratory tract infection, and acute bronchitis were the most common respiratory system diagnoses recorded on medicine claims. In support of these results, the DU90% analysis showed that antimicrobial agents, respiratory system agents, and analgesics, i.e. agents that are mainly used in the management of respiratory infections [42], were the three most prevalent pharmacological classes of medicines claimed with non-specific diagnostic codes. This may suggest a higher prevalence of respiratory diseases than was recorded in our patient population based on specific ICD-10 codes. Respiratory diseases are one of the leading causes of morbidity in children in the general population and represent approximately 25% of primary care consultations [43,44]. The immunosuppression associated with chemotherapeutic agents makes children undergoing cancer treatment more susceptible to respiratory diseases, notable among them being infections [45]. This is confirmed by results of previous studies that indicated the respiratory system as the common site of infections in children on antineoplastic therapy, with respiratory infections representing 16–23% of infectious episodes in these patients [46, 47]. These infections may be from bacterial, viral, or fungal origins [45]. Respiratory infections of bacterial origin, together with possible superinfection of respiratory viral infections with bacteria [48], is supported by the high prevalence of antimicrobial agents. Respiratory viral infections, especially influenza and respiratory syncytial virus infections which are common in immunocompromised children [49–52], are characterized by symptoms such as cold and cough [53,54]. This could also explain the prevalent use of medicines for coughs and colds (63.93%) among the respiratory system agents. The use of analgesics and antipyretics for the management of fever, a primary sign of infection resulting from neutropenia in children receiving chemotherapeutic agents [55,56], could explain the prevalent use of analgesics in this study.

Acute toxicities of the GIT, which include constipation, nausea, vomiting, diarrhea, and susceptibility to gastrointestinal infections, are often associated with cancer chemotherapy [57,58]. Chemotherapeutic agents such as cyclophosphamide are associated with mucosal ulceration, which predisposes patients to gastroenteritis [59]. Gastroenteritis is characterized by diarrhea, nausea, vomiting, and abdominal pain, and is an important cause of morbidity in children especially those who are immunocompromised [60–62]. Mucosal ulceration and its associated gastroenteritis from chemotherapeutic agents are supported by the high proportion of medicine claims associated with gastric ulcer (21.4%) and non-infective gastroenteritis (19.0%) among the diseases of the GIT in

this study. This is also confirmed by the high prevalence of acid reducers among the GIT agents in our population.

The skin is prone to toxicities of chemotherapeutic agents since their mode of action involves targeting rapidly growing cells. Dermatological events, therefore, although rarely life-threatening, are usually reported in patients undergoing chemotherapy [63,64], with skin rashes, hyperpigmentation, and pruritus being the most prevalent condition. This could account for skin disorders being the third most prevalent disease group in our patient population.

The higher proportion of males as compared to females (68.79% vs. 31.21%) in the study population could account for the higher proportion of non-cytotoxic medicine claims in males. A comparison of the prevalence of coexisting conditions in males and females was, however, limited by the incomplete ICD-10 diagnostic codes on medicine claims. The highest proportion of non-cytotoxic medicine claims over the study period in the 5–9 years age group can be attributed to the majority of the study population (34.10%) falling within this age group. The majority of medications classified as CNS agents, musculoskeletal agents, genital system agents, dermatologicals, and urinary system agents, are mostly utilized in the adolescent age group. This may, therefore, account for the high prevalence of these pharmacological classes among the adolescent age group. For example, the high prevalence of acne in adolescents [65] makes the use of acne preparations and contraceptives relatively common in this age group. Contraceptives are also used in the management of menstrual disorders such as amenorrhea and menorrhagia in adolescents [66].

4.1. Study Strengths and Limitations

The study population was drawn from the database of only one PBM company covering a section of the private health sector of South Africa; the results of this study, therefore, cannot be generalized to the whole South African population. The use of the main pharmacological group prescribed as a proxy for diagnoses in cases where medicines were claimed with non-specific ICD-10 diagnostic codes has the potential of introducing bias as some medications may be used for secondary indications or may be used off-label for other conditions not indicated on product labels [67]. Because of our small sample size, our study did not assess the association between the type of cancer and pharmacological drug class on the patient level. The absence of or use of non-specific diagnostic codes further complicated analysis in that change in therapy due to unresponsiveness to a specific drug could not be assessed. Our study also did not assess drugs used in combination or treatment regimens. Because we counted the first claim for every active substance (drug) per patient during the period patients were on treatment for cancer, change in therapy can be misconstrued and lead to the overestimation of the prevalence of a coexisting condition. Under-ascertainment of the prevalence of the use of the various pharmacological classes is, however, also likely because data used for this study were reimbursed claims. Medicine items used by the study population that is not covered under the health plan for which they are subscribed to on their medical schemes are not reimbursed and, consequently, are not included in the database.

Despite the limitations indicated, this study provides preliminary findings of the burden of diseases in children and adolescents

being treated for various childhood cancers. Again, it highlights the utilization patterns of the major pharmacological classes of non-cytotoxic medications for the management of these conditions.

5. CONCLUSION

Most coexisting conditions in children and adolescents on cancer therapy in the section of the private health sector studied were acute conditions and included microbial infections and diseases of the respiratory system. Antimicrobial agents, respiratory system agents, analgesics, ENT and GIT agents were the top five most prevalent pharmacological classes of non-cytotoxic medications utilized by the study population. The high prevalent use of antimicrobial agents in this study indicates the need for the integration of antimicrobial surveillance programs into childhood and adolescent cancer care to curb antimicrobial infections.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

The study was conceived by JRB, MNO, HS and MSL. MSL extracted and analyzed the medicine claims data. MNO interpreted findings and drafted the report under the supervision of JRB. All authors reviewed and approved the final version.

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