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RESEARCH ARTICLE

Intercycle Unplanned Hospital Admissions Due to Cisplatin-based Chemotherapy Regimen-induced Adverse Reactions: A Retrospective Analysis

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Abstract: ***Background*:** Cisplatin is a commonly used chemotherapy agent known to induce serious adverse reactions that may require hospital readmission. We aimed to analyze the extent and factors associated with unplanned hospital admissions due to cisplatin-based chemotherapy regimen-induced adverse reactions.

***Methods*:** Retrospective review of medical records of those patients who received at least one cycle of chemotherapy with cisplatin-based regimen during a six-month period from March to August 2017.

***Results*:** Of the 458 patients who received cisplatin during the study period, 142 patients did not meet inclusion criteria. The remaining 316 patients had a total of 770 episodes of primary admissions for chemotherapy administration. Overall, 187 episodes (24%) of intercycle unplanned hospital admission were recorded of which a major proportion (n=178; 23%) was due to chemotherapy-induced adverse reactions. Underweight patients had higher odds of unplanned admission (OR 1.77, 95% confidence interval [CI] 1.11 to 1.77). Significantly, more number of patients with cancers of head and neck and cancers of musculoskeletal were readmitted (p<0.001). Compared to high-dose cisplatin, low- and intermediate-dose cisplatin had lesser odds of unplanned admission (OR 0.52 and 0.77; 95% CI, 0.31 to 0.88 and 0.41 to 1.45, respectively). Patients without concomitant radiotherapy, drug-drug interaction and initial chemotherapy cycles had lesser odds of unplanned admission (OR 0.38, 0.50 and 0.52; 95% CI, 0.26 to 0.55, 0.25 to 0.99 and 0.32 to 0.84 respectively). Unplanned admissions were mainly due to blood-related (31%) and gastrointestinal (19%) adverse reactions. Among chemotherapy regimens, cisplatin monotherapy (34%) and cisplatin with doxorubicin (20%) regimens resulted in a major proportion of unplanned admissions.

***Conclusion*:** These findings highlight risk factors that help identify high-risk patients and suggest that therapy modifications may reduce hospital readmissions due to cisplatin-based chemotherapy-induced adverse reactions.

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1. INTRODUCTION

Cisplatin is a platinum derivative introduced several decades ago as an antineoplastic agent to treat a myriad of solid tumors. Though the oldest member of its group, it is still a key component of many chemotherapy regimens including those for bladder, head and neck, lung, ovarian, testicular cancers and musculoskeletal tumours [1]. However, among the widely used anticancer drugs, cisplatin is most commonly associated with various forms of adverse reactions. The drug is highly emetogenic, neurotoxic, nephrotoxic, and ototoxic [2]. The incidence rate of cisplatin-induced adverse reactions is as high as more than 90%[2]. Majority of these adverse reactions are usually mild and are self-limiting [3]. Nevertheless, an unknown proportion of these reactions are severe enough to require hospital readmission [4]. Hospital readmissions have been reported in up to 52% of patients who were on cisplatin-based chemotherapy regimen [5, 6]. However, these reports were based on a few specific cisplatin regimens and cancer types rather than cumulative cisplatin-based chemotherapy regimens.

Hospital readmissions are of particular concern because of its significant impact on cost and patient outcomes. Several studies have tried to explore factors that influence hospital readmissions among the general population. Poor care coordination, poor follow-up care, age, female gender, patients of lower socio-economic status, and shorter hospital stay are all known to elevate the risk for readmission [7, 8]. Regarding the causes of readmission, a study [9] analyzed diagnoses of

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potentially avoidable hospital readmissions. It found that in a majority of cases, the readmission diagnoses is a direct or indirect complication of patients' primary diagnoses itself. Interestingly, the same study has found adverse reactions to drugs as one of the most frequent readmission diagnoses. Furthermore, patients with a cancer diagnosis have been reported to have an increased risk of potentially avoidable readmissions compared to other comorbidities [9].

Thus far, a majority of pertinent studies have only focused on hospital readmissions among general medical patients. However, existing evidence suggests that cancer patients, in particular, are more vulnerable to readmission [10]. Among cancer patients, patient characteristics including primary diagnoses, gender, comorbidities, number of previous admissions are all shown to be associated with readmission [10], where most of these factors are non-modifiable. Though reported, many studies have either overlooked or underestimated chemotherapy-induced adverse reactions as a cause of hospital readmission. In our study setting, we observed that among cancer patients, especially those who received cisplatin-based regimen, readmission diagnoses were often associated with adverse reactions. Since adverse reactions are potentially modifiable, readmissions due to adverse reactions could possibly be reduced by knowing the factors associated with it and by introducing appropriate interventions [11]. Generally, to prevent hospital readmissions, healthcare settings are now turning to predictive models in order to identify patients at high risk for readmission and focus resource intensive readmission prevention strategies on such "high-risk" patients [12].

Knowledge of which patients by age, gender, cancer type, cisplatin dose, number of chemotherapy cycle, concomitant drugs or chemotherapy, and drug-drug interactions have the greatest odds of readmission due to adverse reactions is important. This knowledge could help identify high-risk patients and direct the assessment and development of new opportunities to focus on readmissions. Therefore, the aim of this study was to estimate the rate and to investigate those factors associated with intercycle unplanned hospital admissions or readmissions due to cisplatin-based chemotherapy regimen-induced adverse reactions.

2. MATERIALS AND METHODS

This was a retrospective review of medical records of those patients who were diagnosed with any solid tumour and received at least one cycle of chemotherapy with cisplatin monotherapy or cisplatin-based chemotherapy regimen. The study was conducted in a 2300 bedded large tertiary care teaching hospital with established oncology and radiotherapy units. Institutional Review Board approval was obtained prior to initiation of this study.

Patients' medication histories were obtained from the hospital's pharmacy workstation that documents medication transactions of all in-patients and out-patients. Corresponding clinical data were obtained from the electronic medical records containing all hospital admission and readmission data. Unique hospital identity numbers were used to track an individual across pharmacy workstation and electronic medical records.

2.1. Study Population

We identified all patients who received at least one dose of cisplatin over a period of six months between March 2017 and August 2017 from the pharmacy workstation. We excluded outpatients and patients whose clinical and/or pharmacy data were either missing or incomplete. As the intent of the study was to identify various clinical and patient factors associated with hospital readmissions, we included special populations too (for example children, patients with multiple comorbidities and so on), which are typically excluded in other studies.

2.2. Outcome Measures

The primary outcome measure was intercycle unplanned hospital admission due to adverse reactions induced by cisplatin or cisplatin-based regimen. We defined intercycle hospital admission as hospital readmission that occurred between two consecutive chemotherapy cycles during the study period. We intentionally did not use the term '30-dayhospital readmissions' which is widely used in literature for public reporting and comparing hospital readmissions because chemotherapy cycles, in particular, cisplatin regimens, are often given more frequently than 30 days interval [13]. Unplanned admissions for conditions other than those due to adverse reactions including those due to disease exacerbations were grouped separately and not accounted for analysis. Readmissions were attributed to adverse reactions only after conducting causality analysis using WHO-UMC system for standardized case causality assessment [14]. The readmission diagnosis and patient complaints were linked with the chemotherapy regimen administered in the previously planned hospital admission and current medications. Only those readmissions due to adverse reactions that were deemed certain, probable, or possible in the WHO-UMC scale were considered as the primary outcome. More than one unplanned admission within 30 days of discharge was counted separately.

Covariates included patient characteristics, cancer type, cisplatin dose, cisplatin regimen, concomitant drugs or radiotherapy, chemotherapy cycle, drug-drug interactions, and comorbidities. Age wise, patients were grouped into three categories (children ≤18 years; adults <60 years; elderly ≥60 years). According to body mass index (BMI), patients were categorized into underweight (<18.5 kg/m^2), normal weight (18.5 to 24.99 kg/m^2), and overweight/obese (≥25 kg/m^2). Comorbidities were identified and classified into two (patients with no known comorbidities and patients with one or more comorbidities). Cisplatin dose was categorized into low (<60 mg/m^2), intermediate (60 to 99 mg/m^2), and high (≥100 mg/m^2) [15]. Clinically significant drug-drug interactions were also identified after consulting Lexicomp Drug Interaction online tool and Stockley's Drug Interactions (11^{th} edition) and grouped into two including those without drug-drug interactions and those with one or more drug-drug interactions.

2.3. Statistical Analysis

Continuous variables were presented as the mean ± Standard Deviation (SD) or as a median and range, and these were compared using the Student t test or the Mann-

Whitney U test as appropriate. Categorical variables were presented with a number and percentage, and these were compared using the Chi-squared test. We performed logistic regression to analyze the relationship between unplanned hospital admission and variables including age, gender, Body Mass Index (BMI), cisplatin dose, chemotherapy cycle, concomitant radiotherapy, concomitant drugs, drug-drug interaction, comorbidities, and type of cancer. For clinical outcomes, the statistical significance was derived by adjusting the values for potential confounding factors such as patient age, BMI, and comorbidities. A p value of less than 0.05 was considered significant. All analyses were performed with SPSS v16.0.

3. RESULTS

Screening the pharmacy workstation yielded a total of 458 patients who received at least one cycle of cisplatin-containing chemotherapy regimen during the study period. Of these, 142 (31%) patients either received cisplatin in an outpatient/daycare setting or had incomplete information and hence were excluded. The remaining 316 patients resulted in a total of 770 episodes of primary admissions for chemotherapy administration resulting in an average admission rate of 2.44 episodes per patient during the study period. Patients were relatively younger with a mean age of 35.64 ± 17.69 and more likely to be male (66%). In a majority of the episodes, patients received their first chemotherapy cycle (41%) and received low dose cisplatin (47%). In 21% of episodes patients received concomitant cisplatin monotherapy with radiotherapy, while 16% of patients had one or more comorbidities. One or more clinically significant drug-drug interactions were observed in 17.1% of episodes.

The overall intercycle unplanned hospital admission rate was found to be 24% (n=187). After conducting causality analysis, nine readmissions (4.8%) were found due to reasons other than chemotherapy-induced adverse reactions and hence excluded from further analysis. Hence the actual rate of unplanned hospital admission due to a cisplatin-based chemotherapy-induced adverse reaction was 23% (n=178). A majority of these adverse reactions were associated with blood and lymphatic system disorders such as anaemia, neutropenia, thrombocytopenia, and pancytopenia. Patients readmitted due to gastrointestinal disorders developed diarrhoea, nausea, vomiting, gastroenteritis, abdominal pain, dysphagia, and/or anorexia. Metabolism and nutrition disorders included dyselectrolytaemia such as hyponatraemia, hypomagnesaemia, and hypokalaemia. General disorders included acute febrile illness, chills, pain, dizziness, and weakness. Patients readmitted with infection had sepsis or septic shock. Table **1** shows the full demographics and clinical characteristics of patients.

Table 1. Demographics and clinical characteristics of patients.

Characteristics	n	%
Gender		
Men	506	65.7
Women	264	34.3
30-day hospital readmission status		
Readmission due to adverse reactions	178	23.1
Readmission due to other reasons	9	1.2
No readmission	583	75.7
Cisplatin dose		
Low-dose	360	46.8
Intermediate-dose	313	40.7
High-dose	97	12.5
Concomitant radiotherapy		
Yes	162	21.0
No	608	79.0
Concomitant drugs		
Cisplatin monotherapy	176	22.9
One concomitant drug	335	43.5
Two concomitant drugs	251	32.6
Three concomitant drugs	8	1.0
Drug-drug interaction status		
No interactions	638	82.9
Had one interaction	132	17.0

(Table 1) Contd…

Characteristics	n	%
Comorbidities		
No comorbidities	647	84.0
One or more comorbidities	123	16.0
Chemotherapy cycle		
Cycle 1	315	41.0
Cycle 2	190	24.7
Cycle 3	138	18.0
Cycle 4 and above	127	16.5
Cancer types		
Genitourinary and gynecology	250	32.5
Head and neck	158	20.5
Musculoskeletal	114	14.8
Thoracic and respiratory	92	11.9
Brain and nervous system	83	10.8
Gastrointestinal	46	6.0
Endocrine	18	2.3
Others	9	1.2
Adverse reactions		
Blood and lymphatic system disorder	55	30.9
Gastrointestinal disorders	34	19.1
Metabolism and nutrition disorders	28	15.7
General disorders	28	15.7
Infections and infestations	17	9.6
Nervous system disorders	5	2.8
Respiratory	4	2.2
Renal	4	2.2
Others*	3	1.7

*Others included 'immune', 'hepatobiliary', and 'skin'.

3.1. Patient Characteristics and Hospital Readmissions

Age and gender of patients were not found to have a significant association with unplanned hospital admissions. However, patients' BMI was found to have an association (p=0.033). In multivariable analysis, underweight patients were associated with higher odds of readmission (OR 1.77, 95% confidence interval 1.11 to 1.77), whereas overweight and obese patients remained unaffected (p=0.741). The increase in the number of comorbidities was not found to be significantly associated with unplanned hospital admission due to adverse reactions.

Unplanned admission rates varied significantly (p<0.001) by certain types of a cancer diagnosis. Head and neck cancer and musculoskeletal tumours together constituted a significantly high proportion of patients who got readmitted (28.7% and 21.9%, respectively). However, these cancer types constituted only a small proportion of those who did not require readmission due to adverse effects (18.1% and 12.7% respectively) and the difference was found to be statistically significant. As given in Table **2**, other types of cancer did not differ significantly between those who were readmitted and not readmitted.

As shown in Table **3**, after adjusting for patients' clinical and demographic characteristics, we observed a significant variation in adverse reactions-related unplanned admissions across different cisplatin dosages (p=0.01). Referenced by patients who received high-dose cisplatin, the odds ratio for unplanned admission decreased by half for those who received low dose cisplatin (OR 0.52, 95% confidence interval 0.31 to 0.88). Relative to a low dose, the odds ratio for unplanned admission slightly increased for those who received intermediate dose cisplatin but remained below that of high-dose cisplatin (OR 0.77, 95% confidence interval 0.41 to 1.45).

Adverse reactions-induced unplanned admissions were significantly higher among patients who received concomitant radiotherapy (p<0.001). Referenced by patients who received radiotherapy, the odds ratio for unplanned admission was significantly lower for those who did not receive radiotherapy (OR 0.38, 95% confidence interval 0.26 to 0.55).

The number of concomitant drugs had a significant effect on adverse reactions-induced unplanned admissions. The odds of unplanned admission among those who received cisplatin monotherapy was twice as that of those who received one or more concomitant drugs (OR 2.01, 95% confidence

Table 2. Characteristics of 30-day readmission and non-readmission of patients.

Characteristics	Readmission n=178 (%)	No Readmission n=592 (%)	P value
Gender Male Female	113 (63.5) 65 (36.5)	393 (66.4) 199 (33.6)	0.474
Age	37.03 ± 17.10	35.23 ± 17.86	0.233
Cisplatin dose Low dose Intermediate dose High dose	89 (50.3) 55 (31.1) 33 (18.6)	271 (45.8) 258 (43.6) 64 (10.6)	0.002
Concomitant radiotherapy No Yes	116 (65.2) 62 (34.8)	492 (83.1) 100 (16.9)	<0.001
Drug-drug interaction No interaction One or more interactions	159 (89.3) 19 (10.7)	479 (80.9) 113 (19.1)	0.009
Comorbidities No comorbidities One or more Comorbidities	145 (81.5) 33 (18.5)	502 (84.8) 90 (15.2)	0.287
Chemotherapy cycle Cycle 1 Cycle 2 Cycle 3 Cycle 4 and above	84 (47.5) 31 (17.5) 36 (20.3) 27 (14.7)	231 (39.0) 159 (26.9) 102 (17.2) 100 (16.9)	0.040
Concomitant drugs Cisplatin monotherapy One concomitant drug Two or more concomitant drugs	60 (33.7) 65 (36.5) 53 (29.8)	116 (19.6) 270 (45.6) 206 (34.8)	<0.001
Cancer Type Musculoskeletal Genitourinary and gynecology Head and neck Thoracic and respiratory Others*	39 (21.9) 50 (28.1) 51 (28.7) 21 (11.8) 17 (9.6)	75 (12.7) 200 (33.8) 107 (18.1) 71 (12.0) 139 (23.5)	<0.001

*Others included bone and muscle, brain and nervous system, breast, endocrine system, gastrointestinal, haematopoietic and skin.

Table 3. Factors associated with 30-day hospital readmission due to chemotherapy-induced adverse reactions.

Variable	Unadjusted OR	95%CI	P value	Adjusted OR	95% CI	P value
Gender Male Female	0.88 1.00	0.62-1.25 Reference	0.475	1.27 1.00	0.80-2.01 Reference	0.309
Age ≤18 years 19 to 45 years >45 years	1.00 1.04 1.13	Reference 0.66-1.62 0.72-1.77	0.881 0.605	1.00 1.02 1.16	Reference 0.57-1.83 0.61-2.18	0.936 0.655

(Table 3) Contd…

Variable	Unadjusted OR	95%CI	P value	Adjusted OR	95% CI	P value
BMI						
Underweight	1.77	1.77-1.11	0.016			
Overweight/Obese	0.91	0.91-0.53	0.741		NA	
Normal	1.00					
Cisplatin Dose						
Low dose	0.63	0.39-1.02	0.059	0.52	0.31-0.88	0.014
Intermediate dose	0.41	0.24-0.68	0.001	0.77	0.41-1.45	0.415
High dose	1.00	Reference		1.00	Reference	
Radiotherapy						
No radiotherapy was given	0.38	0.26-0.55	<0.001	0.54	1.71-16.90	0.004
Radiotherapy was given	1.00	Reference		1.00	Reference	
Drug-drug interaction						
No Interaction (reference)	1.97	1.18-3.31	0.010	0.50	0.25-0.99	0.048
One or more interactions	1.00	Reference		1.00	Reference	
Comorbidities						
No Comorbidities	0.79	0.51-1.22	0.287	s	NA	
Oneor more Comorbidities	1.00	Reference				
Chemotherapy cycle						
Cycle 1	1.40	0.85-2.30	0.187	0.52	0.32-0.84	0.008
Cycle 2	0.75	0.42-1.34	0.329	0.90	0.55-1.47	0.676
Cycle 3	1.36	0.76-2.41	0.297	0.69	0.40-1.18	0.174
Cycle 4 and above	1.00	Reference		1.00	Reference	
Concomitant drugs						
No concomitant drugs	2.01	1.30-3.10	0.002	2.67	0.80-9.09	0.112
One concomitant drug	0.94	0.62-1.40	0.748	4.32	1.26-14.80	0.020
≥2 concomitant drugs	1.00	Reference		1.00	Reference	
Cancer type						
Musculoskeletal	1.76	0.94-3.27	0.075	0.22	0.11-0.47	<0.001
Genitourinary and gynecology	0.85	0.48-1.51	0.568	0.89	0.40-1.99	0.776
Head and neck	1.61	0.89-2.91	0.113	0.61	0.27-1.37	0.233
Others	0.41	0.21-0.83	0.013	0.26	0.12-0.55	<0.001
Thoracic and respiratory	1.00	Reference		1.00	Reference	

interval 1.30 to 3.10). However, this difference was not found to be statistically significant when adjusted for confounding factors. Drug-drug interactions within the chemotherapy regimen were also significantly associated with adverse reactions-induced unplanned admissions. In multivariable analysis, the absence of interaction was associated with the least odds of unplanned admission (OR 0.50, 95% confidence interval 0.25 to 0.99). Table **4** lists the chemotherapy regimens involving clinically significant drug-drug interactions. Similarly, the odds of unplanned admission steadily increased as the number of chemotherapy cycle increased (for example, OR 0.52, 95% confidence interval 0.32 to 0.84 for the first cycle *vs* the fourth cycle or above).

Among the adverse reactions, 31% of unplanned admission episodes were due to blood-related reactions, whereas gastrointestinal disorders resulted in 19% of unplanned admissions. Other important adverse reactions resulting in unplanned admissions included metabolic disorders, general disorders and infections.

Table 4. List of chemotherapy regimens involving drug-drug interactions.

S. No.	Chemotherapy Regimen	n	%
1	Paclitaxel and cisplatin	53	40.2
2	Docetaxel, cisplatin, and fluorouracil	48	36.4
3	Docetaxel and cisplatin	10	7.5
4	Paclitaxel, ifosfamide, and cisplatin	8	6.0
5	Cetuximab, docetaxel, and cisplatin	8	1.5
6	Bevacizumab, paclitaxel, and cisplatin	5	4.5

Among chemotherapy regimens, cisplatin monotherapy had induced adverse reactions and resulted in unplanned hospital admissions in 34% of episodes. Cisplatin with doxorubicin was the second most common chemotherapy regimen with an unplanned admission rate of 20%. Twenty other regimens contributed to rest of the unplanned admission episodes.

4. DISCUSSION

Cisplatin-induced adverse reactions are very common and are often serious and/orsevere. Cisplatin-based chemotherapy regimens further complicate the clinical stability of patients by exposing them to additional adverse reactions, rendering patients more vulnerable to adverse reactions and contributing to drug-drug interactions. Patients with cancer diagnoses are known to be a cohort with a higher risk of potentially avoidable readmissions, whereas adverse reactions were found to be frequent readmission diagnoses [9]. Cisplatin is one of the most widely used anticancer drugs with relatively greater potency for adverse reactions. The target population in this study included cancer patients who received cisplatin-based chemotherapy regimen during the study period. Moreover, in our clinical practice, we found that cancer patients, in particular, those who were on cisplatin-based chemotherapy regimens were highly susceptible to develop serious adverse reactions that often required hospital readmissions. In this study, we found that intercycle unplanned hospital admissions among patients who received cisplatin-based chemotherapy regimen were very common due to adverse reactions. Among patient characteristics, underweight patients were found more susceptible to adverse reaction-induced unplanned admissions. Other important factors emerging that had a stronger association with unplanned admission included the type of cancer diagnosis, high cisplatin dose, concomitant radiotherapy, drug-drug interactions and number of chemotherapy cycles.

Large retrospective studies have estimated the 30-day readmission rate in cancer patients between5% and 25% [16-18]. In addition, the readmission rate widely differs between types of cancer and different chemotherapy regimens. For example, previous studies have reported 22% readmission rate among patients with gastrointestinal cancers, 13.8% among patients with head and neck cancer, 4.3% among those who underwent lung cancer surgery and 52% in those who received etoposide, ifosfamide, and cisplatin [5, 19, 20]. To the best of our knowledge, ours is the first study of its kind in cancer patients who received cisplatin-based chemotherapy regimens. We found an all-cause unplanned admission rate of 24% in our cohort of patients, whereas the rate due solely to adverse reactions is 23% (95% of overall all-cause readmissions).

One study reported a hospital readmission rate of 31% due to cisplatin-induced adverse reactions [6]. But in this study, the cohort was limited to those with head and neck cancer receiving low-dose cisplatin concurrent with radiotherapy. Although the readmission rate is almost similar to what we have found, our study results are more generalizable with respect to age, cisplatin regimen, type of cancer and concurrent radiotherapy.

In contrast to the general population, age was not found to influence unplanned hospital admissions in our target population. A recent large retrospective analysis [21], which included patients with all conditions, explored a nonlinear association with age, in which the likelihood of readmission was elevated for children transitioning to adulthood. However, it is interesting to note that our results are similar to that reported in the literature when the cancer cohort alone is considered [22]. Neither gender was found significantly associated with unplanned admission due to adverse reactions in our study population, unlike Hispanic and Taiwanese cancer patients in whom male gender had a higher risk of all-cause readmission [22, 23]. This study underscores the importance of body weight in unplanned admissions. Previous studies have shown that overweight and obese patients are at higher risk for all-cause readmission in both adults and children with different conditions including heart failure [24-26]. However, in stroke patients the opposite has been reported in which readmission rate was significantly lower among overweight and obese patients, whereas significantly higher in underweight patients when compared to normal weight patients [27]. Our study results concur with those of stroke patients in which underweight patients had a higher risk, whereas overweight and obese patients were at a lesser risk for readmission compared with that of normal weight patients.

Our study results showed that half of those admitted patients had one or more comorbidities, but this factor was not found to have a significant association with adverse reaction-induced unplanned admission in our cohort. Manzano et.al.reported that patients with three or more comorbidities and or metastatic disease had a higher risk of readmission [28]. However, our cohort significantly varied with respect to the number of comorbidities. In our cohort, a majority of

patients had either one or two comorbidities and rarely more than two. This variation might explain the difference in effect which needs further investigation to find the true effect of this factor.

Generally, patients with concomitant medications are perceived to have a higher risk of adverse reaction-induced readmissions. However, we observed a paradoxical effect of higher odds of readmissions in cisplatin monotherapy group when compared to those with one or more concomitant medications. The administration of concomitant radiotherapy might help to explain the increased odds of unplanned admission observed in the cisplatin monotherapy group. In the monotherapy group, patients received radiotherapy in 98% of episodes compared to that of 2.5% in the other group. Previous studies have shown that radiotherapy could possibly increase the severity of chemotherapy-induced adverse reactions [29].

Patients in our study were more likely to be readmitted due to blood-related adverse reactions followed by gastrointestinal disorders and electrolyte imbalance. We attributed the adverse reactions to cisplatin regimen by conducting a causality assessment using one of the commonly used tools, WHO-Uppsala Monitoring Centre tool. Previous studies using informal assessment methods have been known to report artificially inflated numbers of adverse reactions [30]. In addition, the pattern of adverse reactions in our study corroborates with those reported in the product and medical literature [31]. Though chemotherapy-induced adverse reactions are very common, they are poorly reported or documented in medical records. Specific comprehensive medical terminologies such as SNOMED-CT and MedRA are used to document adverse reactions by adverse event reporting systems including MedWatch and VigiFlow. However, most of the electronic medical record systems use International Classification of Diseases (ICD) codes for documenting diagnoses which are not sensitive enough for capturing specific drug-induced adverse reactions. Hence, direct identification of adverse reactions reliably from most of the currently available electronic medical record data sources is not feasible. In this study, we indirectly identified chemotherapy-induced adverse reactions from electronic medical records by conducting a causality analysis using readmission diagnoses data and drugs administered in the previously planned hospital admission and current medications.

As reported earlier [11], we also found an increased risk for readmission among patients who had drug-drug interactions. As established chemotherapy regimens were used, a majority of the patients had no drug-drug interactions while a relatively small proportion (17%) had not more than one interaction. Altogether, 29 chemotherapy regimens were used in the study population. However, only six regimens included drugs with clinically significant interactions. In all these interacting regimens, cisplatin interacted with either paclitaxel or docetaxel. It is established that platinum derivatives such as cisplatin enhance the myelosuppressive effect of taxane derivatives such as docetaxel and paclitaxel.

Our initial motivation for this investigation was to identify those factors that increase the risk for hospital readmission between two adjacent chemotherapy cycles. Upon completion of our analyses, we recognized that certain factors such as BMI, cisplatin dose, concomitant radiotherapy, drug-drug interactions, number of chemotherapy cycle, concomitant drugs, and cancer type can probably have a substantial impact on intercycle hospital admissions due to adverse reactions. However, age and gender did not have any influence on hospital readmission in our cohort. For clinical decision making the purpose, a more suitable approach for readers would be to consider consulting more similar studies preferably those using prospective methods to complement this data.

5. IMPLICATIONS FOR PRACTICE

Adverse reactions and unplanned hospital admissions among cancer patients have serious repercussions. Previous reports impart a significant number of patients either delaying or refusing further chemotherapy because of adverse reactions and related hospital readmissions [32]. One study has reported a significant reduction in survival rate among patients who delayed chemotherapy administration primarily due to adverse reactions [6]. Despite preventive steps including premedication, electrolyte preloading, clinical monitoring, and patient counselling, a significant number of patients receiving cisplatin-based chemotherapy regimen end up being readmitted due to adverse reactions. Identifying high-risk patient set would potentially aid the multidisciplinary healthcare team to plan, create or modify protocols and focus on further reducing the incidence of unplanned hospital admissions due to adverse reactions. Some of the associated factors found in this study such as cisplatin dose and drug-drug interaction are modifiable factors which imply a possible reduction of unplanned admission rate if proper attention is given to the high-risk patient group. Other associated factors such as BMI, concomitant radiotherapy and cancer type though are not modifiable, unplanned admissions could be potentially reduced by taking alternate measures (*e.g*. dose reduction). This could be of interest to hospital administrators as well considering the huge cost incurred by health systems or patients towards adverse reactions-related hospital admissions.

6. LIMITATIONS

This study has some limitations. This is a single center study in a tertiary care teaching hospital. The data sources used in this study are not comprehensive in data capturing. For example, information pertaining to any readmissions if occurred outside the study center were not included in the data source due to the lack of a national patient identifier system. However, to compensate for this limitation, we excluded patients with incomplete study data. This factor may have an effect on the final results. In addition, we did not analyze cancer stage, tumor size, or lymph node involvement, and radical intent of treatment of patients which are all associated with higher rates of readmission. Nevertheless, the association of these factors with increased risk of adverse reactions is not known.

CONCLUSION

Intercycle unplanned hospital admission due to adverse reactions was very common among patients receiving cisplatin-based chemotherapy regimen. The study findings high-

light risk factors for readmission that may help identify high-risk patients who are more likely to be readmitted. In addition, the results suggest that therapy modifications based on associated factors coupled with other prophylactic clinical and non-clinical interventions may help reduce hospital readmission rate in these patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board (IRB Min No: 10928 [Retro] dated 25.10.17).

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are avalible from the corresponding author (H.B.R.) on reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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