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Measurement of Cumulative Drug Exposure from Clinical Data Warehouse

Mathilde BORIES^{a,1}, Aurélie BANNAY^b, Morgane PIERRE-JEAN^a,
Guillaume BOUZILLE^a and Pascal LE CORRE^{c,d,e}.

^a *Université de Rennes, CHU de Rennes, INSERM, LTSI-UMR 1099, Rennes, France*

^b *Université de Lorraine, CHRU de Nancy, Centre national de la recherche scientifique, Inria, Laboratoire lorrain de recherche en informatique et ses applications, Nancy, France*

^c *Pôle Pharmacie, Service Hospitalo-Universitaire de Pharmacie, CHU de Rennes, Rennes, France*

^d *Laboratoire de Biopharmacie et Pharmacie Clinique, Faculté de Pharmacie, Université de Rennes, Rennes, France*

^e *Université de Rennes, CHU de Rennes, Inserm, EHESP, Irset UMRS 1085, Rennes, France*

ORCID ID: Mathilde BORIES <https://orcid.org/0000-0001-9092-4298>

Abstract. Polypharmacy (PP) and hyperpolypharmacy (HPP), are prevalent among cancer patients and are associated with an increased risk of drug-drug interactions (DDI) and potentially inappropriate medications (PIM). This study aimed to characterize PP, HPP, DDI, and PIM in patients with hematological malignancies hospitalized for hematopoietic stem cell transplantation (HSCT) by introducing a novel metric: cumulative drug exposure. Clinical data warehouse (CDW) records were employed to develop algorithms that quantified patients' cumulative exposure to these prescribing determinants during hospitalization. This entailed determining the number of days during the hospital stay when the patient was exposed to PP, HPP, PIM and/or DDI. For PIM and DDI, the number of PIMs or DDIs administered per day was taken into account in this calculation. Among 339 HSCT patients, PP and HPP were highly prevalent (over 67% of HSCT patients), almost all patients experienced DDI (over 98% of HSCT patients) and almost all elderly patients were exposed to PIM (over 98% of HSCT patients). Cumulative drug exposure differed between allogeneic and autologous HSCT patients, with allogeneic patients being more exposed to HPP (28.5 days vs 4.7 days for autologous HSCT patients) and DDI (255.6 days vs 58.4 for autologous HSCT patients). This study proposes a novel approach to assessing the impact of prescribing determinants on patient outcomes and provides insights for future research into the association between drug exposure and adverse events. Indeed, the use of cumulative drug exposure as a metric provides a comprehensive view of patient exposure throughout hospitalization, thereby enhancing understanding of the impact of prescribing practices on clinical outcomes.

Keywords. Clinical data warehouse, hematopoietic stem cell transplantation, polypharmacy, hyper polypharmacy, drug-drug interactions, potentially inappropriate medications.

¹ Corresponding Author: Mathilde Bories; E-mail: mathilde.bories@univ-rennes.fr.

1. Introduction

Polypharmacy (PP) and hyperpolypharmacy (HPP) refer to the administration of five to nine drugs per day and ten or more drugs per day, respectively [1]. These prescribing determinants are prevalent in cancer patients and appear to be risk factors for drug-drug interactions (DDI) [2]. DDI occur when the exposure and/or the pharmacological effect of one drug is altered by the concomitant administration of another one. DDI are a major concern in oncology due to the iatrogenic risk they pose. Additionally, in elderly patients, PP and HPP can lead to the prescription of potentially inappropriate medications (PIM), which are drugs whose risks outweigh the expected benefits, and also entail a risk of iatrogenic events [3]. Therefore, it seems appropriate to precisely quantify the exposure to PP, HPP, DDI and PIM in cancer patients.

Clinical data warehouses (CDWs) are invaluable for this purpose because they facilitate extensive reuse of drug administration data, enabling longitudinal analysis of drug exposure. This capability contrasts with primary-care settings, where exposure is typically inferred from prescriptions or dispensations. CDW data empower researchers to delve deeper than mere prevalence, gaining profound insights into the patterns and impacts of drug use over time. However, leveraging CDW data for measuring drug exposure necessitates the implementation of specific strategies, given that they were not originally designed for this purpose. To address this, our study aimed to propose a new metric for characterizing several important prescribing determinants: PP, HPP, DDI and PIM. This novel metric designated as cumulative drug exposure, is a quantitative measure of the total number of days during which a patient is exposed to these prescribing determinants during their hospital stay.

The methodology for calculating cumulative drug exposure was developed through a use case study involving patients hospitalized for hematological malignancies treated with hematopoietic stem cell transplant (HSCT) using data collected from Rennes University Hospital CDW (eHOP).

2. Methods

Patients hospitalized at Rennes University Hospital for allogeneic or autologous HSCT between November 1, 2020, and December 31, 2023, were selected via the eHOP CDW based on their diagnosis-related group. Data collected included patient information and hospital stay details, such as age, admission and discharge dates, total length of stay, date and type of HSCT and diagnosis. Detailed drug administration data were also collected, including the date and time, drug name, dosage, route of administration, UCD code (codification used by the French hospital information system to identify a drug) and ATC class (the anatomical therapeutic chemical classification system).

For each patient, the number of different drugs administered per day was calculated, representing the number of different ATC classes administered on the same day. This allowed us to determine whether the patient was in PP (5 to 9 drugs per day) or HPP (more than 10 drugs per day) status for each day.

The Theriaque database, was used to detect DDI [4]. Theriaque defines a DDI as an interaction between two drugs, which can occur between two ATC classes or two UCD codes. Theriaque categorizes DDI into four severity levels: contra-indicated, should be avoided, precaution of use, and to take into account. A previous study has enabled us to map these severity levels into two categories: major (contra-indicated, should be

avoided) and moderate (precaution of use, and to take into account) [5]. We searched for potential DDI for each drug administration identified in eHOP, considering a DDI present if two interacting drugs were administered on the same day. All severity levels (major and moderate) were considered and for each patient the presence of a DDI and the number of these DDIs per day were determined.

The GO-PIM list, specific to geriatric oncology patients, was used to identify PIMs [6]. A drug was considered as a PIM if the patient was 65 or older and the drug's ATC class was listed in GO-PIM. This enabled us to ascertain and quantify the number of PIMs per day for each elderly patient.

The aforementioned methods for detecting PP, HPP, PIM and DDI enabled us to estimate the prevalence of patients for each prescribing determinants (proportion of patients with at least one day of exposure during their hospital stay). This allowed us to compare allogeneic and autologous HSCT patients using a chi-squared test. Moreover, these methods permitted the calculation of patients' cumulative drug exposure to these prescribing determinants, namely the number of days during the hospital stay when the patient was exposed to PP, HPP, PIM and/or DDI. For PIM and DDI, the number of PIMs or DDIs administered per day was taken into account in this calculation (For example, four DDI during one hospital day was considered equivalent to four days of exposure). Additionally, the cumulative drug exposure adjusted for length of stay (cumulative exposure density) was calculated. The two types of HSCT (allogeneic and autologous) were compared with regard to cumulative drug exposure and cumulative exposure density using the Wilcoxon test. A p-value of less than 0.05 was considered to be statistically significant.

3. Results

This study included 339 patients of which 122 had an allogeneic HSCT and 217 an autologous HSCT. Patients with allogeneic HSCT had a mean age of 52.2 years old (26 were ≥ 65 years old), while those with autologous HSCT had a mean age of 57.2 years old (61 were ≥ 65 years old). The average hospital length of stay was 39.5 days (33.8 days for ≥ 65 years old patients) for allogeneic HSCT and 17.3 days (15.8 days for ≥ 65 years old patients) for autologous HSCT. Prevalence, cumulative drug exposure and cumulative exposure density of each prescribing determinants according to the type of HSCT are presented in table 1 and table 2 respectively.

Table 1. Prevalence (percentage of patients) with PP, HPP, DDI and PIM during hospitalization.

	Allogeneic HSCT (n = 122)	Autologous HSCT (n = 217)	p-value
PP	98.4 (n = 120)	98.6 (n = 214)	> 0.9
HPP	99.2 (n = 121)	67.7 (n = 147)	< 0.001
DDI	100.0 (n = 122)	98.6 (n = 214)	0.2
• Major	95.1 (n = 116)	25.4 (n = 55)	0.6
• Moderate	100.0 (n = 122)	98.6 (n = 214)	< 0.001
PIM	100.0 (n = 26)	98.4 (n = 60)	0.6

Table 2. Cumulative drug exposure in days and cumulative exposure density (cumulative drug exposure adjusted to hospital length of stay) of PP, HPP, DDI and PIM during hospitalization.

Cumulative drug exposure (in days)	Allogeneic HSCT	Autologous HSCT	p-value
PP	9.1	9.0	0.2
HPP	28.5	4.7	< 0.001
DDI	255.6	58.4	< 0.001

• Major	10.1	1.6	< 0.001
• Moderate	245.6	56.9	< 0.001
PIM	33.7	15.7	< 0.001
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<i>Cumulative exposure density</i>	Allogeneic HSCT	Autologous HSCT	p-value
PP	0.2	0.5	< 0.001
HPP	0.7	0.3	< 0.001
DDI	6.1	3.3	< 0.001
• Major	0.2	0.1	< 0.001
• Moderate	5.9	3.2	< 0.001
PIM	1.0	1.0	0.6

4. Discussion

The collected data indicates that over 67% of HSCT patients were exposed to PP or HPP during their stay. Additionally, almost all patients were exposed to DDI and all elderly patients were exposed to PIM. These results are concordant with the literature reporting high prevalence of PP, DDI and PIM in HSCT patients [7][8]. Prescribing determinants were also defined by calculating cumulative drug exposure. Allogeneic HSCT patients were highly exposed to HPP, DDI and PIM and slightly exposed to PP (9.1 days of exposure to PP over a 39-day hospital stay vs 28.5 days of exposure to HPP). Autologous HSCT patients were exposed to PP more than to HPP in proportion of their length of stay (9.0 days vs 4.7 day over a 17-day hospital stay). Allogeneic patients are exposed to a higher number of drugs and DDI per day compared to autologous HSCT patients [9]. This could explain why their cumulative drug exposure in terms of HPP and DDI is significantly more important than for autologous patients.

To our knowledge, this study is the first to suggest using cumulative drug exposure to describe PP, HPP, DDI, and PIM. This new metric based on CDW exploitation provides a more accurate description of real-life drug-use by focusing on drug administration rather than prescription and allows for analysis throughout the entire hospital stay, rather than just at admission or discharge. Moreover, calculating cumulative drug exposure in terms of the number of exposure days has several advantages over simple prevalence measures. It provides a more precise assessment of both the intensity and duration of drug exposure, facilitates detailed longitudinal analysis, and enhances risk stratification by distinguishing between short-term and long-term exposures. This method could also enable comparative studies and the evaluation of public health interventions, potentially leading to improved predictive models and more personalized treatment strategies.

Indeed, this study is an initial investigation into the potential association between drug exposure and negative outcomes such as death, rehospitalization, or adverse biological events. Currently, the literature data demonstrate, with some variation, that prescribing determinants have an impact on the clinical outcome of HSCT patients. The use of PP and/or PIM and/or DDI was associated with survival and clinical events to varying degrees depending on the study [7][8][10]. However, except for one study [8], the prescribing determinants were evaluated at the time of HSCT and did not consider all potential patient exposure during hospitalization. Pharmacoepidemiological studies have highlighted the importance of considering the duration of patient exposure when investigating the association between drug exposure and adverse events, rather than

limiting exposure to a binary measure [11]. Therefore, the use of a metric such as cumulative drug exposure, as presented in this study, could provide additional insight into the associations between PP, HPP, DDI or PIM and negative outcomes. Finally, these results underscore the necessity of interdisciplinary collaboration, combining expertise in medical informatics and pharmacy to accurately analyze data and enhance patient health outcomes. By integrating diverse skills from pharmacoepidemiology to health informatics, we could develop more precise predictive models and personalized treatment strategies.

5. Conclusions

This study has highlighted the usefulness of CDW in describing the exposure of hospitalized patients to multiple prescribing determinants. The completeness and reliability of the data allowed for the calculation of the cumulative drug exposure of HSCT patients to PP, HPP, DDI and PIM. This new metric of exposure will enable more precise analysis of the association between drug exposure and the clinical outcome of HSCT patients.

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