



Original article

Trigger tools are as effective as non-targeted chart review for adverse drug event detection in intensive care units

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ABSTRACT

Objective: This study aimed to compare the use of trigger tools and non-targeted chart review as methods for the detection of adverse drug events in an intensive care unit considering the health system of a developing country.**Methods:** Patients were divided in groups that were submitted to different methods (trigger tool and non-targeted chart review) for adverse drug event detection. Medical records were retrospectively reviewed, and adverse drug events detected during the data collection were analyzed by a multidisciplinary team and classified according to their causality, predictability, severity and damage level.**Results:** The search for adverse events performed by trigger tools and non-targeted chart review allowed the identification of similar numbers of events (61.09 and 64.04 ADE/1000 patient-days, respectively), types of event and related drugs. In both groups, the most frequently detected adverse events were related to metabolic, gastrointestinal, cardiovascular and hematological systems. These organic systems matched the drugs most associated with adverse event occurrence: anti-infectives, antithrombotics and insulins. Events identified by non-targeted chart review presented higher causality relationships and were considered less severe than those observed by trigger tool use ($p < 0.05$).**Conclusion:** The similar performance between these methods supports trigger tool applicability in the ICU routine, as this methodology requires less time to retrieve information from the medical records.© 2018 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Pharmacotherapy has been described as a significant cause of morbidity and mortality and is directly related to the occurrence of adverse events (Bürkle et al., 2013). Patients in critical care are more vulnerable to Adverse Drug Event (ADE) occurrence. Characteristics inherent to their clinical condition complexity, monitoring devices, invasive procedures and greater use of medicines, especially those with narrow therapeutic indexes or those administered by the parenteral route, make them more susceptible to damages resulting from pharmacological therapy (Leape et al., 1999; Kane-Gill et al., 2012).

Since the ADE occurrence is affected by several determinants, Intensive Care Unit (ICU) rates vary from 5.1 to 87.5 ADE/1000 patient-days (Wilmer et al., 2010). The Critical Care Safety Study, conducted at an academic tertiary hospital in the United States, found a rate of 80.5 adverse events/1000 patient-days, of which 47% were drug-related, 2% had a fatal outcome and another 12% threatened patients' lives (Rothschild et al., 2005). This data heterogeneity found in the literature is mainly related to methodological differences regarding the definition of adverse event used and the strategies employed upon ADE detection (Wilmer et al., 2010).

In most institutions, the primary method for obtaining information about ADE occurrence is voluntary case reporting, which presents underreporting as one of its main limitations (Ratz et al., 2010; Lopez-González et al., 2009). Chart review, another approach for detecting ADE, has been considered the gold standard for determining their frequency since it involves a comprehensive and detailed scan of the medical record data performed by experienced healthcare professionals. An alternative to make the chart review more feasible is to examine the files by selecting signs that could indicate the occurrence of ADE, as in the Trigger Tool for Measuring

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Adverse Drug Events. This method, developed from the Institute for Healthcare Improvement, presents a retrospective chart review using clues that alert the reviewer to the possibility of harm. The triggers are selected sentinel trackers that structure the data collection process, guiding ADE detection using a small number of selected triggers, performed over a short period of time (Rozich et al., 2003). Thus, the trigger tool is an easy-to-use method to identify ADEs and to measure their incidence rates, and its implementation does not require high levels of technological or financial resources (Griffin and Resar, 2009).

Taking into consideration previous reports regarding trigger tool and non-targeted chart review sensitivities for detecting ADEs, this article aims to compare the application of such methods for ADE detection in the ICU, considering the routine of a health service in a developing country.

2. Methods

2.1. Design

This is a descriptive, retrospective study that aimed to compare the use of trigger tools and non-targeted chart review as methods for the detection of ADEs that occurred in an ICU from 01 September 2015 to 30 April 2016 (8 months).

The operational definition of ADE adopted in this study considered an ADE as an injury resulting from medical intervention related to a drug. Under this definition, the term ADE included harm caused by adverse drug reactions and from medication errors (Morimoto et al., 2004; World Health Organization, 2009; NCCMERP, 2015).

2.2. Setting

A medical ICU of a tertiary public hospital in the Brazilian Midwest was used for this study. This 229-bed hospital has 40 ICU beds, which are divided into three medical wards and one surgical ward, and they admit approximately 1100 patients per year, referred by hospital wards or external units that are part of the national public health system, mainly from the Midwest, North and Northeast regions of the country.

Multidisciplinary assistance was provided by medical staff, including the departments of nursing, physiotherapy, phonoaudiology, nutrition, dentistry, psychology, social service and clinical pharmacy. Multidisciplinary rounds were held daily, conducted by the coordinating physician, with the purpose of discussing each patient's clinical case, outcomes and therapeutic strategies.

The ICU had its performance indicators evaluated prior to the selection of the wards that would participate in this study to ensure uniformity among the study groups. The selected units presented similarities in occupancy rates, length of stay, readmission, death, care-related infections, and they were identified as wards A and B. These wards also presented similar patient profiles (i.e., clinical or infectious complications from medical specialties such as cardiology, nephrology, pneumonology or gastroenterology), infrastructure, technological resources, staff allocation, care provided, consumed medicines and other medical supplies. Despite the fact that this institution had three ICU wards, the third ward was not considered in this study because the service routine was being restructured, and its characteristics differed from those of wards A and B.

2.3. Sample

Patients considered eligible for this study were older than 18 years, with lengths of stay higher than 24 h, and agreed to participate by signing a consent form. Patients admitted to the ICU for

surgical recovery were excluded due to the existence of a specific ward for this purpose and to clinical/epidemiological differences from those patients at the evaluated units. Participant allocation between groups (A and B) took into consideration only the ICU ward, which was determined by the bed availability at the admission time.

2.4. Data collection

Two experienced ICU clinical pharmacists performed data collection. Several training sessions were performed as a pretest before the record review to mitigate variability. Data were retrospectively obtained after patient discharge, comprising the entire period of the ICU stay. To characterize the sample, the following variables were considered: demographics (age and gender), length of stay, cause of ICU admission, primary diagnosis and comorbidities, and the prognostic scores *Simplified Acute Physiology Score* (SAPS3) (Metnitz et al., 2005; Moreno et al., 2005) and *Sequential Organ Failure Assessment* (SOFA) (Vincent et al., 1996).

The following methods were used for ADE detection in the groups formed (A and B):

- Group A: all participants' electronic medical charts were manually searched for the medication module triggers (M1-M13), according to the *IHI Global Trigger Tool for Measuring Adverse Events (Second Edition)* (Griffin and Resar, 2009). This tool consists of a 20-minute scan per medical record to select signs or clues that identify possible ADEs, triggering an in-depth investigation to confirm the ADE. Triggers related to medication use include abrupt interruption of medication use, prescription of an antagonist, or an abnormal laboratory test result.
- Group B: all medical charts were comprehensively reviewed for possible ADEs. These files were retrospectively reviewed for an explicit reporting of the occurrence or hypothesis of an ADE, along with signs and symptoms described in the medical record that were not identified as an ADE by the assisting team but were considered by the reviewers as possibly related to drug use (Gregory and Radovinsky, 2012). The electronic medical records consisted of sections containing documents such as medical and multidisciplinary progress notes, prescriptions, laboratory tests, vital signs monitoring records, admission and discharge summaries.

After data collection, suspected ADEs were presented to a multidisciplinary team consisting of a nurse, a pharmacist and a physician. Scheduled meetings sought to discuss the data collected and to reach consensus on ADE confirmation and classification. If there were divergent interpretations, medical records were reviewed by this team until inter-rater agreement was achieved.

Each possible ADE detected was intensively evaluated by the multidisciplinary team regarding the temporal connection with the medicine use, properties of the suspected drug and the patient's clinical condition to confirm the adverse event. Events were classified considering their causality according to Naranjo's Algorithm (Naranjo et al., 1981), Rawlins & Thompson's predictability criteria (Rawlins and Thompson, 1991), severity according to the Common Terminology Criteria for Adverse Events v4.0 – CTCAE (National Cancer Institute, 2010) and damage level according to the NCCMERP Index for Categorizing Medication Errors (National Coordinating Council for Medication Error Reporting, 2001).

2.5. Statistical analysis

Data were recorded in a database using EPI Info® v.7.1 (Centers for Disease Control and Prevention – CDC, 2015), and all statistical

tests were performed using IBM® SPSS® Statistics v. 22 (IBM Corp., 2015). The normal distribution was verified using the Kolmogorov-Smirnov test, and continuous variables were analyzed using the Mann-Whitney *U* test. Categorical variables were analyzed using Pearson's chi-square test. *P*-values < 0.05 were considered statistically significant.

3. Results

During the data collection period, 331 participants were admitted to the study, distributed between group A (trigger tool, 162 participants) and group B (non-targeted chart-review, 169 participants). There were no significant differences in age, gender, ICU length of stay and clinical outcomes between groups (*p* > 0.05), as shown in Table 1.

In both groups, ICU admissions were mainly caused by respiratory, cardiovascular and renal complications (Table 2). In group A, the most frequent causes of hospitalization were J18.9 - Pneumonia, unspecified organism (12.37%) and J96.0 - Acute respiratory

failure (12.37%); in Group B, the same clinical conditions predominated: J18.9 (11.83%) and J96.0 (10.65%). As shown in Table 2, the prognostic scores SAPS3 and SOFA, used to predict mortality during hospitalization, did not present differences between groups (*p* > 0.05).

The two wards' samples presented similar clinical and epidemiological characteristics, confirming the similarity of management indicators and other observed characteristics that corroborate the homogeneous distribution of patients on the ICU wards selected as study groups.

The methods used to detect ADE revealed their similar capacities to identify the events. The maximum ADE/participant value was verified in a subject from group A who experienced 5 events, whereas one member of group B was identified with 4 ADEs. Compared to the trigger tool, non-targeted chart review was able to establish a drug-event causality as "Probable" or "Defined" in a greater proportion of the detected events (*p* = 0.001); these events also presented lower severity according to the CTCAE classification (*p* = 0.029). There were no differences in predictability and damage level between events detected by each method (*p* > 0.05) (Table 3).

The trigger tool identified 98 ADEs, with 18 different types of events; the most frequent were bleeding episodes (detected by the triggers "Abrupt hemoglobin reduction > 4 g/dL", "International Normalized Ratio > 6" and "Partial thromboplastin time > 100 s"), hypotension (triggered by "Hypotension report") and hypoglycemia (screened by "Glycemia lower than < 50 mg/dL"). Although there was no specific trigger for hypokalemia, during the search for other triggers, 10 cases were identified and counted according to this method's original recommendation.

The 122 ADEs detected by non-targeted chart review were distributed among 25 different types of events, and episodes of hypoglycemia and bleeding were among the most frequent in group A. In group B, there was greater detection of drug-induced kidney injury (14) and electrolyte disorders (19) that included changes in serum sodium or potassium concentrations (Table 4).

The main causes of ADEs were drugs with therapeutic targets in the cardiovascular system, regardless of the detection method used. The use of the trigger tool enabled the identification of ADEs caused by 44 different drugs, with 5 of these drugs accounting for 44.90% of the cases (44 of the 98 ADEs in the Group A): Heparin (15), Insulin Regular (11), Furosemide (9), and the systemic antibacterials Piperacillin + Tazobactam (5) and Vancomycin (4).

The ADEs detected in the group B participants' medical charts were assigned to 48 different drugs, most frequently due to the use of Insulin Regular (13), Heparin (7), Vancomycin (7), Furosemide (6), Amikacin (6) and Hydrocortisone (6), accounting for 36.89% of the events identified in this group. ADEs caused by other drug classes are described in Table 5.

Table 1

Demographic characteristics of the patients admitted to an intensive care unit of a tertiary hospital in the Brazilian Midwest, Brazil, 2016.

	Trigger tool	Non-targeted chart review	<i>p</i>
Eligible patients	162	169	-
Gender			
Male (%)	84 (51.85%)	94 (55.62%)	0.492 ^a
Female (%)	78 (48.15%)	75 (44.38%)	
Age, median (IQR)	67.50 (49.50–76)	65 (50–75.50)	0.442 ^b
Length of stay, median (IQR)	7 (4–11)	8 (5–13)	0.191 ^b
ICU outcome			0.370 ^a
Discharge	112 (69.14%)	109 (64.50%)	
Death	50 (30.86%)	60 (35.50%)	
Patient-days	1604	1905	-

IQR: interquartile range.

^a Pearson's chi-square test for independence.

^b Mann-Whitney *U* test for independent variables.

Table 2

Main admission causes in the intensive care unit of a tertiary hospital in the Brazilian Midwest, categorized according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (World Health Organization, 1992) and prognostic scores. Brazil, 2016.

	Trigger tool	Non-targeted chart review	<i>p</i>
ICD-10			0.972 ^a
J00-J99 Diseases of the respiratory system	56 (34.57%)	55 (32.54%)	
I00-I99 Diseases of the circulatory system	29 (17.90%)	34 (20.12%)	
N00-N99 Diseases of the genitourinary system	26 (16.05%)	29 (17.16%)	
K00-K93 Diseases of the digestive system	17 (10.49%)	16 (9.47%)	
A01-B99 Certain infectious and parasitic diseases	12 (7.41%)	15 (8.88%)	
Other ICD-10 codes	22 (13.58%)	20 (11.83%)	
SAPS3, median (IQR)	61 (48.50–73)	61(49–73)	0.892 ^b
SOFA at ICU admission, median (IQR)	5 (2.50–8)	5 (2–10)	0.726 ^b

SAPS3: Simplified Acute Physiology Score (Metnitz et al., 2005; Moreno et al., 2005); SOFA: Sequential Organ Failure Assessment (Vincent et al., 1996).

^a Pearson's chi-square test for independence.

^b Mann-Whitney *U* test for independent variables.

4. Discussion

The methods used in this study (trigger tool and non-targeted chart review) provided similar detections of ADEs, considering the number of events and the affected organic systems. The similarity of these methods' performance had already been described in the first studies using trigger tools (Resar et al., 2003; Resar et al., 2006; Rozich et al., 2003; Classen et al., 2011). However, this similarity is not a consensus among the articles already published (Franklin et al., 2010). Some studies conducted using trigger tools were not focused on this comparison, since they do not apply a chart review to identify the actual occurrence of an ADE in the evaluated population (Kenneley et al., 2013; Sharek et al., 2011).

The incidence density rates of events detected using trigger tool and non-targeted chart review (61.09 and 64.04 ADE/1000 patient-days) were close to 70.1 ADE/1000 patient-days described in a

Table 3

Classification of the adverse drug events detected in the intensive care unit of a tertiary hospital in the Brazilian Midwest, Brazil, 2016.

	Trigger Tool	Non-targeted chart review	<i>p</i>
Adverse drug events	98	122	–
Patients experiencing adverse drug events (%)	65 (40.12%)	73 (43.19%)	0.321 ^a
Cumulative incidence (ADE/patient)	0.60	0.72	–
Incidence density rate (ADE/1000 patient-days)	61.09	64.04	–
Causality: Naranjo algorithm (Naranjo et al., 1981)			0.001 ^a
<0 points: Doubtful	–	–	
1–4 points: Possible	28 (28.57%)	12 (9.84%)	
5–8 points: Probable	63 (64.29%)	95 (77.87%)	
>9 points: Definite	7 (7.14%)	15 (12.29%)	
Severity: CTCAE v4.0 (National Cancer Institute, 2010)			0.029 ^a
Grade 1: Mild, asymptomatic, intervention not indicated	7 (7.14%)	17 (13.93%)	
Grade 2: Moderate, requires local or noninvasive intervention	36 (36.74%)	48 (39.34%)	
Grade 3: Severe, not immediately life-threatening, prolongs hospitalization	32 (32.65%)	45 (36.89%)	
Grade 4: Life-threatening, requires urgent intervention	23 (23.47%)	12 (9.84%)	
Grade 5: Death related to adverse event	–	–	
Predictability: (Rawlins and Thompson, 1991)			0.991 ^a
Type A: Dosing-dependent, predictable	86 (87.76%)	107 (87.70%)	
Type B: Pharmacologically unexpected, idiosyncratic	12 (12.24%)	15 (12.30%)	
Damage: NCC MERP Index for Categorizing Medication Errors (National Coordinating Council for Medication Error Reporting, 2001)			0.099 ^a
Category E: Temporary harm to the patient and required intervention	55 (56.12%)	62 (50.82%)	
Category F: Temporary harm to the patient and prolonged hospitalization	24 (24.49%)	46 (37.70%)	
Category G: Permanent patient harm	2 (2.04%)	3 (2.46%)	
Category H: Intervention necessary to sustain life	17 (17.35%)	11 (9.02%)	
Category I: Patient death	–	–	

CTCAE: Common Terminology Criteria for Adverse Events version 4.0.

^a Pearson's chi-square test for independence.

multicenter study performed in a North American medical ICU (Smithburger et al., 2015). Other previous studies suggest that the frequency of adverse events in critically ill patients may range from 13.8 to 116.8 ADE/1000 patient-days (Anthes et al., 2013; Benkirane et al., 2009; Cullen et al., 1997; Kane-Gill et al., 2012; Rothschild et al., 2005). This range can be explained by the difference in the methods used for event detection: voluntary reporting underestimates the event rate, whereas active surveillance strategies (such as those used in our study) are capable of increasing detection rates.

Cardiovascular ADEs were frequently detected by both methodologies used in this study; however, the use of trigger tools was more likely to detect episodes of hypotension within these cardiac complications ($p = 0.003$). The early identification of this event can prevent complications such as cognitive alterations, kidney failure, and ischemic events and can allow the development of strategies to minimize healthcare-related risks. The greater detection of these hypotension episodes in the trigger tool group may be related to the presence of a specific trigger for this physiological variable, which makes the event detection process more structured than non-targeted chart review (Griffin and Resar, 2009; Kane-Gill et al., 2014; Klopotoska et al., 2013).

Structuring the data collection process, as in the chart review targeted by the use of trigger tool, can restrict the amount and variety of the detected ADE to the events of higher incidences since this methodology is characterized by guiding ADE detection using a small number of selected triggers. Non-targeted chart review results in a comprehensive data collection and provides the detection of non-specific or unusual events by performing a broad evaluation of clinical signs and laboratory findings (Franklin et al., 2010). This is observed in the present study due to the diversity of events detected, such as hypothyroidism, phlebitis and bradycardia, along with the greater detection of corticosteroid-related adverse events ($p = 0.035$).

The corticosteroid-related events detected by the non-targeted chart review included episodes of hyperglycemia, cardiovascular and electrolyte alterations (hyponatremia and hypokalemia); such

events were pharmacologically predictable, as reported by Sprung et al. (2008) and Bissell et al. (2015). In contrast to what has been reported in the literature, infections resulting from immunosuppression or gastrointestinal bleeding that could be associated with the use of these medicines were not identified (Bissell et al., 2015; Narum et al., 2014).

The methods used have identified cardiovascular drugs, systemic antibacterials, insulins and antithrombotic agents as major causes of ADEs. These findings were similar to data reported by Joshua et al. (2009), who verified the greater frequency of events related to the use of antimicrobials and cardiovascular agents, especially events related to the use of Furosemide. Reis and Cassiani (2011) also identified, among the main causes of events, those resulting from these drug classes and medicines directed to the hematological and neurological system.

Frequent use of Insulin and anticoagulants in the ICU, inherent to critical care practice, may increase the risk of serious ADE. These medicines are rated as high-alert medications by the Institute for Safety Medication Practice (2014) because they bear a greater risk of causing serious and permanent harm in cases of misuse. The frequency of this medication group among the events detected by the trigger tool, as verified in our study, corroborates the Institute for Healthcare Improvement recommendation to use trigger tool as a preferred strategy for detecting adverse events related to high-alert medications by monitoring blood coagulation, hypoglycemia, hypotension and excessive sedation (Institute for Healthcare Improvement, 2012).

Even with the similar characteristics of events detected in both groups, the use of trigger tools was not able to identify the variety of ADEs that were detected in the non-targeted chart review. This difference is because certain methods for ADE detection are more sensitive than others when considering different types of events (Kane-Gill et al., 2012). Despite the fact that non-targeted chart review has been considered the gold standard for determining the frequency of ADEs, some characteristics make it an imperfect referential, including its inconsistency and lack of information on the record, its subjectivity or inter-rater variations in data

Table 4

Adverse drug events detected in an intensive care unit in the Brazilian Midwest: classification as to the affected organic system, according to the Common Terminology Criteria for Adverse Events-CTCAE v4.0 (National Cancer Institute, 2010). Brazil, 2016.

Organic system Adverse drug event	Trigger Tool	Non-targeted chart review	<i>p</i>
Metabolism and nutritional disorders	31 (31.63%)	44 (36.07%)	0.835 ^a
Hypoglycemia	14	19	
Hypokalemia	10	10	
Hyperkalemia	4	5	
Hyperglycemia	2	4	
Hypernatremia	1	3	
Hypothyroidism	–	2	
Hyponatremia	–	1	
Gastrointestinal disorders	13 (13.27%)	19 (15.57%)	0.877 ^a
Diarrhea	6	8	
Vomiting	6	7	
Constipation	1	3	
Nausea	–	1	
Cardiac disorders	17 (17.35%)	14 (11.47%)	0.003 ^a
Hypotension	16	6	
Hypertension	1	4	
Bradycardia	–	4	
Blood and lymphatic system disorders	17 (17.35%)	12 (9.84%)	0.102 ^a
Bleeding [†]	17	12	
Renal and urinary disorders	7 (7.14%)	14 (11.47%)	0.277 ^a
Acute kidney injury	7	14	
Nervous system disorders	6 (6.12%)	4 (3.28%)	0.389 ^a
Depressed level of consciousness	5	4	
Tremor	1	–	
Investigations	3 (3.06%)	6 (4.92%)	0.635 ^a
Platelet count decreased	2	3	
Altered liver function [‡]	1	3	
Other	4 (4.08%)	9 (7.38%)	0.414 ^a
Rash	3	2	
Phlebitis	–	3	
Delirium	1	1	
Fever	–	1	
Dyspnea	–	1	
Myalgia	–	1	

[†] In the original CTCAE classification, haemorrhagic adverse events are categorized according to the site of bleeding (for example: esophageal varices hemorrhage, gastrointestinal adverse event). In this table all hemorrhagic events were classified as hematological disorder, regardless of the bleeding site.

[‡] It comprises alterations of the following laboratory parameters: elevation of alanine-aminotransferase, elevation of aspartate-aminotransferase, elevation of blood bilirubin, elevation of alkaline phosphatase and elevation of gamma-glutamyltransferase.

^a Pearson's chi-square test for independence.

acquisition process, the reviewer training requirement and the time consumption involved for complete document inspection (Miguel et al., 2013; Smithburger et al., 2015). However, structuring the search for adverse events using a trigger tool allows time savings, the possibility of automating the search and adapting the triggers to the characteristics of each institution (to increase the sensitivity and specificity for several types of expected events), making this methodology more feasible for continuous application in the hospital routine (Muething et al., 2010).

ADEs detected using trigger tools and non-targeted chart review were different considering their causality and severity classification ($p < 0.05$). The use of the Naranjo Algorithm aims to establish a causal relationship between drug administration and ADE onset, reducing subjectivity in the analysis of the event, and considering elements described in the scientific literature regarding the event,

Table 5

Drugs that caused adverse drug events in an intensive care unit in the Brazilian Midwest: classification according to Anatomical Therapeutic Chemical Classification-ATC Index (World Health Organization, 2016). Brazil, 2016.

ATC Classification (1st level, anatomic group) (2nd level, therapeutic group)	Trigger Tool	Revisão de Prontuário	<i>p</i>
A. Alimentary tract and metabolism	20 (20.41%)	28 (22.95%)	0.538 ^a
A02 Drugs for acid related disorders	2	2	
A06 Drugs for constipation	3	5	
A10 Drugs used in diabetes	15	16	
Other ATC Codes (A01, A04, A12)	–	5	
B. Blood and blood forming organs	22 (22.45%)	16 (13.11%)	0.816 ^a
B01 Antithrombotic agents	21	15	
B05 Blood substitutes and perfusion solutions	1	1	
C. Cardiovascular system	27 (27.55%)	32 (26.23%)	0.324 ^a
C01 Cardiac therapy	6	9	
C02 Antihypertensives	6	4	
C03 Diuretics	12	9	
Other ATC Codes (C07, C09, C10)	3	10	
G. Genitourinary system and sex hormones	1 (1.02%)	–	–
G04 Urologicals	1	–	
H. System hormonal preparations, excl. sex hormones and insulins	2 (2.04%)	8 (6.56%)	0.035 ^a
H01 Pituitary and hypothalamic hormones and analogues	1	–	
H02 Corticosteroids for systemic use	1	8	
J. Anti-infectives for systemic use	13 (13.26%)	27 (22.13%)	0.144 ^a
J01 Antibacterials for systemic use	12	27	
J05 Antivirals for systemic use	1	0	
N. Nervous system	12 (12.24%)	10 (8.20%)	0.821 ^a
N01 Anesthetics	2	2	
N02 Analgesics	5	3	
N05 Psycholeptics	2	3	
Other ATC Codes (N03, N04)	3	2	
R. Respiratory system	1 (1.02%)	1 (0.82%)	0.157 ^a
R03 Drugs for obstructive airways diseases	–	1	
R06 Antihistamines for systemic use	1	–	

^a Pearson's chi-square test for independence.

including the timing relationship and the history and clinical characteristics of the patient (Naranjo et al., 1981). The relevance of these aspects in the Naranjo Algorithm categorization and the greater scope and detail of the information acquired by non-targeted chart review allowed 90.16% of the events detected by this method to be classified as high causality (probable or definite), while scores above 5 points were only reached in 71.43% of the events detected by trigger tools ($p = 0.001$).

The predominance of mild- and moderate-severity events (National Cancer Institute, 2010) detected by non-targeted chart review (53.27%) may also be justified by the possibility of the reviewer's critical analysis of more information, which makes this technique a more sensitive method for ADE detection. In contrast, the predominance of severity degrees 3 and 4 events detected through the use of trigger tool is justified by targeting the detection on high-alert medications, and defining reference values to identify a potential ADE makes it possible to detect these events only when changes in clinical and laboratory parameters have already reached alarming levels.

The fact that trigger tools detected fewer renal events supports the inferences above. The trigger "rising BUN or serum creatinine

greater than 2 times baseline” requires at least acute kidney injury (AKI) stage 2 to detect each ADE. In contrast, the non-targeted chart review detected these renal events more frequently, since this method is able to identify earlier stages of acute kidney injury (medical record finding of increases 1.5- to 1.9-fold above the baseline; a ≥ 0.3 mg/dL absolute increase in serum creatinine can indicate stage 1 AKI) (Bellomo et al., 2004; National Cancer Institute, 2010).

Among the limitations experienced during this study, the fact that it was developed in a single hospital can be taken into account. To attenuate this design feature, the study was conducted using distinct ICU wards. Using different wards in the same hospital made it possible to reduce clinical and epidemiological discrepancies between the studied groups and to lower external interferences on the evaluated ADE detection methods.

5. Conclusion

The methods applied in this study, respecting their particularities, allowed the detection of similar amounts of ADE, types of event and related drugs, and how they differed in the events' causality and severity classification. The group submitted to non-targeted chart review presented greater diversity of collected data and identified events, whereas the use of trigger tools focused the ADE detection on the triggers investigated.

The similar performance between these methods supports the use of trigger tools in the ICU routine. The lower amount of time required to acquire information from medical records, the possibility of automated search and adaptation of triggers to local pharmacoepidemiology are features for better applicability of this method, especially in suboptimal conditions for health services, such as those provided in developing countries.

Conflict of interests

The authors declare no conflict of interest.

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Ethical approval

Hospital Alberto Rassi Ethics Committee on Research approved this study by report number 1,177,803. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard. Informed consent form was obtained from all individual participants included in the study. If the invited patient was vulnerable or had reduced decision-making ability, the consent was obtained from his legal responsible.

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