

Accuracy of triggers in the identification of adverse drug events in hospitalized elderly

Acurácia de gatilhos na identificação de eventos adversos a medicamento em idosos hospitalizados

Precisión de los factores desencadenantes en la identificación de eventos adversos por medicamentos en ancianos hospitalizados

Received: 12/12/2020 | Reviewed 12/17/2020 | Accept: 12/20/2020 | Published: 12/26/2020

Chriscia Jamilly Pinto de Sousa

ORCID: <https://orcid.org/0000-0002-6996-7717>

Federal University of Pará, Brazil

E-mail: jamillysousa@ufpa.br

Ana Cristina Lo Prete

ORCID: <https://orcid.org/0000-0002-2874-5296>

São Judas Tadeu University, Brazil

E-mail: ana.loprete@saojudas.br

Carolina Heitmann Mares Azevedo Ribeiro

ORCID: <https://orcid.org/0000-0002-9457-2733>

Federal University of Pará, Brazil

E-mail: carolmheitmann@hotmail.com

Abstract

Objective: Evaluate trigger accuracy for identifying adverse drug events (ADEs) in hospitalised elderly. Methods: Two hundred patients ≥ 60 years old from a medical clinic within a private hospital were followed-up. For ADE identification the adapted Global Trigger Tool tracker methodology was used. Causality was determined using the Naranjo Algorithm. Results: Of the 200 elderly patients included in the study, 106 were females (53%), the average age was 79 years, and the average length of hospital stay was approximately ± 10 days. Selected triggers were identified 1,457 times. The group of triggers with the best performance regarding its analysis accuracy was evolution triggers, with sensitivity of 69% and positive predictive value of 68%. In the individual performance analysis, the evolution tracker allergy, allergic reaction, pruritus achieved 100% performance for both sensitivity and positive predictive value. A total of 165 ADs were identified. Of these, 18% were phlebitis and 16% were hypoglycaemia. Drugs associated with ADE

included insulin (15%) and Clarithromycin (9%). Conclusion: The triggering methodology has been effective for identifying ADEs. In addition, determination best trigger for constructing an ADE identification tool for hospitalised elderly was performed.

Keywords: Drug-related side effects and adverse reactions; Pharmacovigilance; Quality indicators, health care; Aging.

Resumo

Objetivo: Avaliar a acurácia dos gatilhos para identificar eventos adversos a medicamentos (EAM) em idosos hospitalizados. Métodos: Duzentos pacientes ≥ 60 anos de uma clínica médica de um hospital privado foram acompanhados. Para a identificação do EAM, foi usada a metodologia do rastreador da *Global Trigger Tool* adaptada. A causalidade foi determinada usando o algoritmo de Naranjo. Resultados: Dos 200 idosos incluídos no estudo, 106 eram do sexo feminino (53%), a idade média foi de 79 anos e o tempo médio de internação foi de aproximadamente ± 10 dias. Os gatilhos selecionados foram identificados 1.457 vezes. O grupo de gatilhos com melhor desempenho quanto à acurácia da análise foi presente nas evoluções, com sensibilidade de 69% e valor preditivo positivo de 68%. Na análise de desempenho individual, o gatilho de alergia, reação alérgica e prurido obteve desempenho de 100% tanto para sensibilidade e valor preditivo positivo. Um total de 165 eventos adversos foram identificados. Destes, 18% eram flebite e 16% eram hipoglicemia. Os medicamentos associados ao EAM incluíram insulina (15%) e claritromicina (9%). Conclusão: A metodologia de uso de gatilhos tem se mostrado eficaz na identificação de EAM. Além disso, foi realizada a determinação do melhor gatilho para a construção de uma ferramenta de identificação de EAM para idosos hospitalizados.

Palavras-chave: Efeitos colaterais e reações adversas relacionados a medicamentos; Farmacovigilância; Indicadores de qualidade em assistência à saúde; Envelhecimento.

Resumen

Objetivo: Evaluar la precisión del disparador para identificar eventos adversos por medicamentos (AAM) en ancianos hospitalizados. Métodos: Se siguió a 200 pacientes ≥ 60 años de una clínica médica de un hospital privado. Para la identificación del ADE, se utilizó la metodología de seguimiento adaptada *Global Trigger Tool*. La causalidad se determinó mediante el algoritmo de Naranjo. Resultados: De las 200 personas mayores incluidas en el estudio, 106 eran mujeres (53%), la edad promedio fue de 79 años y la estancia hospitalaria promedio fue de aproximadamente ± 10 días. Los desencadenantes seleccionados se

identificaron 1.457 veces. El grupo de desencadenantes con mejor desempeño en términos de precisión de análisis fue el desencadenante de evolución, con una sensibilidad del 69% y un valor predictivo positivo del 68%. En el análisis del desempeño individual, la alergia, reacción alérgica y picazón evolutiva logró un desempeño del 100% tanto para la sensibilidad como para el valor predictivo positivo. Se identificaron un total de 165 EA. De estos, el 18% eran flebitis y el 16% hipoglucemiantes. Los medicamentos asociados con ADE incluyeron insulina (15%) y claritromicina (9%). Conclusión: Se ha demostrado que la metodología de activación es eficaz para identificar la IAM. Además, se llevó a cabo la determinación del mejor desencadenante para la construcción de una herramienta de identificación de ADE para ancianos hospitalizados.

Palabras clave: Efectos colaterales y reacciones adversas relacionados con medicamentos; Farmacovigilancia; Indicadores de calidad de la atención de salud; Envejecimiento.

1. Introduction

The World Health Organisation (WHO) (2002) has defined an adverse event (AE) as any incident that results in unintended damage arising from care and unrelated to the natural evolution of a patient's disease. The occurrence of an adverse drug event (ADE) is one of three main explanations for AE (Mendes, Martins, Rozenfeld, & Travassos, 2009). For this reason, the WHO (2017) launched the third global challenge for patient safety: harmless medication to reduce the prevalence of ADE in the world.

The use of medicines is essential in health care. Medicines are used to prevent and treat several pathologies, and are responsible for enhancing quality of life (Gomes, Silva, & Galvão, 2017). Despite this, there are risks related to this technology that must be considered by the health team, institutions and health authorities in order to create barriers that prevent adverse events. ADE are associated with damage to patient health, increased length of hospital stay and increased health service costs (Almeida, Castro, & Caldas, 2011).

In the United States of America (USA), adverse events are the third leading cause of death, and at least one medication error occurs per day in each hospitalised patient (Makary & Daniel, 2016). These errors, despite being preventable, can cause AEs. Thus, hospitalised patients are particularly susceptible to the occurrence of ADE (Charles, 2010).

Some factors predispose patients to ADE including extremes of age, clinical severity, comorbidities and the use of polytherapy. These factors characterise geriatric patients as an at risk group for the occurrence of ADEs (Silva, Ribeiro, Klein, & Acurcio, 2012). Physiological

changes that occur throughout the aging process also interfere in pharmacokinetic and pharmacodynamic processes, and predispose this age group to toxicity, drug interactions and adverse events. In addition, the geriatric population is one of the most medicalised group in society due to self-medication, a high incidence of chronic degenerative diseases and progressively decreasing functional capacity (Carvalho *et al.*, 2012; Pizzol *et al.*, 2012).

Some strategies of active searching have been used to identify and prevent ADE. Among these, we highlight triggers, which are features of the medical records of patients that may indicate the presence of ADEs. Various triggers have been described in the literature. The Institute developed the “Global Trigger Tool” (GTT) for Healthcare Improvement (IHI) and uses retrospective analysis of medical records to monitor AEs. Health institutions for implementing safer practices and improving procedures use this data. The prospective use of this tool produced variable results for AE identification (Griffin & Resar, 2009). This study aims to evaluate the accuracy of use of triggers in the identification of adverse drug events (ADEs) in hospitalised elderly patients.

2. Methods

Study setting and subjects

This observational and prospective study was conducted from August to December of 2018, in a 150-bed private hospital in Belém-Pa, Brazil. The Ethics and Research Committee of the Federal University of Pará (code number 97957518.4.0000.00186) approved this research.

Inclusion criteria were as follows: patients aged ≥ 60 years old, admitted to the hospital's medical clinic during the mentioned period, with a hospital stay longer than 48 hours. Where the patient and/or legal guardian agreed to participate in the study by signing the informed consent form. Exclusion criteria included all patients with communication difficulties, patients in contact isolation, or patients with no clinical outcome. Throughout the study period, there were 461 hospitalisations. Of these, 90 were not elderly and 39 met exclusion criteria.

A sample calculation determined that 179 of the total 332 eligible elderly patients would be required to produce 95% confidence. Data presented in this work correspond to 200 elderly people monitored and randomly selected using the program BioStat®. In this work, the WHO (2009) definition of ADE was used, which states that ADE is defined as “any

incident resulting from the process of using drugs that result in damage or injury to the patient, including adverse drug reactions and medication errors”.

Triggers

Was used Triggers from the medication module of the Global Trigger Tool methodology, as shown in Chart 1, proposed by Griffin & Resar (2009). In addition, Chart 2 describes clinical changes identified in a study by Silva (2017), which were adapted as triggers in the present study. The triggers that correspond to medicines were considered present when they were both prescribed and administered (as noted by the nursing team).

Chart 1. IHI trigger for the “Medicines” module.

Chart 1. IHI triggers from the medication module of Global Trigger Tool methodology.

IHI triggers Identification	Trigger Identification according to the study site standardisation	Clinical alteration to consider triggers and positive ADE according to IHI
M1 - Positive test for <i>Clostridium difficile</i> with a history of Antibiotic	Laboratory Testing: <i>Clostridium difficile</i> .	Positive examination of <i>Clostridium difficile</i> associated with antibiotic use and diarrhoea
M2 - Activated partial thromboplastin time (aPTT) > 100 seconds	Laboratory Testing: aPTT	aPTT > 100 seconds, using heparin with bleeding
M3 - International normalized ratio (INR) index > 6.	Laboratory Testing: INR	INR > 6, with bleeding
M4 - Blood glucose < 50mg/dL.	Vital signs: • Glycaemia (Capillary/serum) Mutliprofessional Evolution • Hypoglycaemia • Lethargy • Weakness	Intervention to treat blood glucose > 50mg/dL with symptoms (weakness and/or lethargy) in patients using insulin and/or hypoglycaemic agents
M5 - Serum creatinine twice above the baseline	Laboratory Testing: • Creatinine 2x above the baseline	Creatinine 2x above baseline associated with nephrotoxic drugs
M6 - Vitamin K administration	Medication: • Administration of Vitamin K	Vitamin K administration and bleeding recorded
M7 - Diphenhydramine administration	Medication: • Diphenhydramine administration	Diphenhydramine administration for allergic reaction intervention
M8 - Flumazenil administration	Medication: • Flumazenil Administration	Administration of flumazenil, due to severe hypotension or prolonged sedation
M9 - Naloxone administration	Medication: • Naloxone Administration	Naloxone administration with signs and/or symptoms related to the use of narcotics (except illicit use of drugs and overdose)

M10 - Antihemetic administration	Medication: <ul style="list-style-type: none"> • Dimenhydrate + pyridoxine + glucose + fructose • Bromopride • Metoclopramide • Ondansetron 	Antihemetic administration due to nausea or vomiting that interferes with feeding, postoperative recovery or produces late discharge
M11 – Hypotension/excessive sedation	Mutliprofessional Evolution <ul style="list-style-type: none"> • Hypotension • Sedation • Lethargy • Dizziness Vital signs: <ul style="list-style-type: none"> • Blood pressure $\leq 90/60$ mmHg. (VII Brazilian Guidelines on Hypertension, 2016) 	Positive record of hypotension related to administration of sedative, analgesic or muscle relaxant
M12 – Abrupt discontinuation of medicines	Medication: Abrupt and/or sudden stop in medication use	Abrupt and/or sudden stop in medication use, except antibiotics and/or administration route modification

Source: Griffin and Resar (2009).

Chart 2. Suggested triggers according to Silva (2017).

Chart 2. Suggested trigger according to Silva, 2017.

Triggers Identification	Trigger Identification according to the study site standardisation	Clinical alteration to consider triggers and positive ADE according to IHI
Corticosteroid Administration.	Medication: <ul style="list-style-type: none"> • Prednisolone • Methylprednisolone • Dexamethasone • Hydrocortisone 	Administration of corticosteroids associated with an allergic reaction
Antihistamine Administration	Medication: <ul style="list-style-type: none"> • Cetirizine • Desloratadine • Dexchlorpheniramine • Hydroxyzine • Promethazine 	Administration of corticosteroids associated with an allergic reaction
Respiratory Rate < 12rpm	Vital signs: <ul style="list-style-type: none"> • Respiratory frequency < 12rpm (Potter & Perry, 2013) 	Change in respiratory rate related to the use of sedatives
Heart rate ≤ 50 bpm	Vital signs: <ul style="list-style-type: none"> • Heart rate ≤ 50 bpm (Pastore <i>et al.</i>, 2009) 	Change in heart rate related to the use of sedatives

	Multiprofessional Evolution <ul style="list-style-type: none"> • Bradycardia 	
Tremors (Sobrafo, Anvisa 2011)	Multiprofessional Evolution <ul style="list-style-type: none"> • Tremor 	Record of tremor associated with specialised intervention for hypoglycemia
Constipation (Lindberg <i>et al.</i> , 2011)	Multiprofessional Evolution <ul style="list-style-type: none"> • Constipation 	Registration of the word constipation associated with the use of opioids
Diarrhoea (Farthing <i>et al.</i> , 2013)	Multiprofessional Evolution <ul style="list-style-type: none"> • Diarrhoea "and/or" dysentery " 	Registration of the word diarrhoea and/or dysentery associated with the use of antibiotics
Hemorrhagia (Balderas <i>et al.</i> , 2011)	Multiprofessional Evolution <ul style="list-style-type: none"> • Bleeding, petechia, purpura, haematuria, haematochezia, melena, haematemesis, epistaxis, haemoptysis, haematoma Laboratory Testing: <ul style="list-style-type: none"> • Haematocrit < 30% • Absolute reduction in haematocrit \geq 10% 	Registration of one of the words in medical records and/or positive identification in laboratory exam
Hyperglycaemia (Brazilian Diabetes Society Guidelines, 2017)	Multiprofessional Evolution <ul style="list-style-type: none"> • Hyperglycaemia Laboratory Testing: <ul style="list-style-type: none"> • Blood glucose (serum). Vital signs: <ul style="list-style-type: none"> • Glycaemia (capillary) 	Registration of the word hyperglycaemia and/or glycaemia \geq 140mg/dL (capillary or serum) associated with hyperglycaemic drugs
Hypertension (VII Brazilian Guidelines on Hypertension, 2016)	Multiprofessional Evolution <ul style="list-style-type: none"> • Hypertension Vital signs: <ul style="list-style-type: none"> • Blood pressure \leq 90/60mmHg 	Registration of the word hypertension and/or blood pressure \leq 90/60mmHg associated with hypertensive drugs
Liver damage (Temple, 2006)	Multiprofessional Evolution <p>Change in mental state (encephalopathy) in patients without cirrhosis.</p> Laboratory Testing: <ul style="list-style-type: none"> • Bilirubin at least twice concomitant with transaminases elevation at least three times, without 	Encephalopathy record and/or laboratory test trigger associated with hepatotoxic drugs

	elevation of alkaline phosphatase or INR	
Kidney injury (Nephrology, 2012)	Multiprofessional Evolution <ul style="list-style-type: none"> Worsening kidney function Laboratory Testing: <ul style="list-style-type: none"> Increase in creatinine by 50% above baseline for more than 7 days Increase in creatinine by 0.3mg/dL for at least 2 days 	Record of evolution trigger and/or laboratory test triggers related to the use of nephrotoxic drugs
Nausea and vomiting (Paliativos, 2011)	Multiprofessional Evolution <ul style="list-style-type: none"> Nausea and/or vomiting 	Identification of nausea and/or vomiting associated with medication administration
Skin rash (Iannini <i>et al.</i> , 2006)	Multiprofessional Evolution <ul style="list-style-type: none"> Rash and/or itching and/or allergy and/or allergic reaction. 	Registration of one of the triggers in the multiprofessional evolution.
Tachycardia (Pastore <i>et al.</i> , 2009)	Heart rate ≥ 100 bpm (beats per minute).	Heart rate recording ≥ 100 bpm associated with drugs that cause tachycardia.
Phlebitis	Multiprofessional Evolution <ul style="list-style-type: none"> Phlebitis 	Registration of phlebitis associated with infusion of irritating and/or vesicant medication.

Source: Authors.

Data Collection

All patient data were assessed by two independent (pharmacists) reviewers. If there was doubt and/or disagreement regarding the occurrence of an ADE, a third reviewer (physician) was consulted. Reviewer training was carried out using a training programme provided by IHI, which taught reviewers to use the Global Trigger Tool. The frequently asked questions section also was used to answer questions that arose during training. A pilot study was carried out with 50 patients to make necessary adjustments to the data collection tool. Results obtained during the pilot study were not considered in this study.

Data collection involved the following four stages. Stage 1 involved the identification of hospitalised elderly patients. The Hospital Census Report of the MV SOUL® Management System was used to identify patients. This report allowed researchers to access a list hospitalised patients that included the following patient data: date of birth, name, attending physician, medical care number, and date of hospitalisation. Subsequently, the inclusion and

exclusion criteria were applied to define which elderly patients could be considered for participation in the research.

Stage 2 involved the acquisition of patient consent. After 48 hours of hospitalisation, a bed visit to each patient was made, and research objectives were explained. At this time, patients were asked to provide informed consent.

In Stage 3, patients were monitored. At the same time, patients answered a questionnaire during an interview. Information collected included life and physiological habits and continuous medication use. The patients were monitored daily during their entire period of hospitalisation using an MV PEP® system, which allowed researchers to view prescriptions, laboratory tests and access team evolutions to search for triggers. Data was recorded on a Google form.

Stage 4 involved determining causality of trigger. After recording information determined during Stage 3, strength of the cause of each ADE was determined using clinical evidence provided in the event causality chain algorithm, which was previously described in Naranjo *et al.* (1981). A duration not exceeding 20 minutes was used, as recommended by the IHI. All the technical information regarding medicine was determined using the Micromedex Solution® System.

Statistical Analysis

The determination of the accuracy of triggers in the identification of ADE was performed using measurements of sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV). These values were set individually for each tracker and for trigger groups. Sensitivity was defined as the proportion of patients with an ADE that were identified by the tracker and patients with an ADE that was not identified by the tracker. PPV was defined as the proportion of ADEs identified by the tracker and the number of unidentified patients who experienced ADEs. Specificity was defined as the proportion between patients who did not have ADE and in the presence of any tracker compared to patients who had the tracker, but did not have ADE. While NPV was the proportion among patients who had neither ADE nor the presence of a tracker for patients who presented ADE, but was not identified by a tracker. Statistical analyses were performed using BioStat® Software and all analyses, parameters were considered significantly different when $p < 0.05$.

3. Results

The average age of the 200 patients selected was 79 years old, and 106 (53%) were female. The average length of each patient's hospital stay was 10 days, and patients who had ADEs had an average stay of 12 days, compared the 6-day average that was determined for patients who did not experience an ADE. Eighty-two patients (41%) were hospitalised due to an infectious condition. The non-specific urinary tract infection (UTI) was the most prevalent International Classification of Disease category in patients assessed, and occurred in 15% (30/200) of hospitalisations considered.

Regarding comorbidities, 98% (196) of the elderly patients considered had at least one comorbidity. Among the most prevalent diseases observed, we highlight: systemic arterial hypertension (SAH), diabetes mellitus, and malignant neoplasia. Due to the high incidence of comorbidities, 91% (182) of patients reported using at least one medication continuously. During hospitalisation, an average of 14 prescriptions, 162 doses of medication, and 14 different active ingredients were provided per patient. The distribution of pharmacotherapeutic risk was as follows: 65%, 29%, and 6% of elderly patients were classified to be at moderate, high, or low risk, respectively.

Trigger Identification Accuracy

In this study, the triggers occurred 1.457 times (\square 7.2) in 99.5% (199) of the elderly hospitalised patients considered. Of these, 13.7% (200) of related triggers corresponded to 76% (125/165) of ADEs identified the survey, and other ADEs were identified without a trigger.

The absence of triggers was observed in only one patient throughout the duration of hospitalisation. Selected triggers occurred 1,457 (one thousand four hundred and fifty-seven) times, and an average of 7.2 triggers were observed per patient. Of these, 200 (13.72%) were related to the occurrence of an ADE. Sensitivity and PPV were established both for groups of triggers and for each trigger individually. In individual analyses of triggers, sensitivity varied between 0.92 and 1.0 and NPV varied between 0.32 and 1.0. The lowest NPVs were associated with the following triggers: blood glucose > 140mg/dL (capillary or serum, 0.32); Blood pressure < 140/90mmHg (0.46), Heart rate > than 100 bpm (0.72). Other triggers had NPVs over 0.92.

Triggers were placed in the following categories: medication, evolution, laboratory tests and vital signs. The following triggers did not occur in patients during the study period: medicines (cetirizine, dexchlorpheniramine, flumazenil, naloxone and prednisolone); evolution (arrhythmia and tremor); laboratory tests (international normalised ratio (INR) > 6, positive test for *Clostridium difficile*; and haematocrit > 30% or absolute reduction in haematocrit \leq 10%. Meanwhile, the all vital signs trigger was identified at least once.

In addition, the following identified triggers were not associated with ADEs, which made it impossible to determine Sensitivity and PPV: medicines (bromopride, dexamethasone, dimenhydrat, methylprednisolone, metoclopramide, and Vitamin K); evolution (insomnia, hypertension, and dizziness); laboratory tests (creatinine increase greater than 50% of the baseline for more than 7 days; time of activated partial thromboplastin (aTTP) > 100 s; increase of bilirubin 2x the elevation of transaminases, without elevation of alkaline phosphatase and INR \geq 1.5); vital signs (blood pressure < 140/90 mmHg).

Medication module trigger prediction accuracy

An individual analysis of the medication group revealed sensitivity values between 0.17 and 0.67 and PPVs between 0.02 and 1.0. The best parameter for identifying ADE was the diphenhydramine trigger (sensitivity, 50%; PPV, 100%). Despite having a sensitivity value of 67%, hydrocortisone had a low PPV (10%). Table 1 includes values other sensitivity and PPV measurements.

Table 1. Accuracy of triggers within the medicament module.

TRIGGER MEDICATIONS	S		E		PPV		NPV	
	N	%	n	%	n	%	n	%
Bromopride	-	-	0.93	93%	-	-	0.99	99%
Desloratadine	0.25	25%	0.92	92%	0.07	7%	0.98	98%
Dexamethasone	-	-	0.94	94%	-	-	0.98	98%
Diphenhydramine	0.50	50%	1.0	100%	1.0	100%	0.99	99%
Dimenhydrinate	-	-	0.94	94%	-	-	0.99	99%
Hydrocortisone	0.67	67%	0.80	80%	0.10	10%	0.99	99%
Hydroxyzine	0.17	17%	1.0	100%	1.0	100%	0.97	97%
Methylprednisolone	-	-	0.98	98%	-	-	0.98	98%
Metoclopramide	-	-	0.99	99%	-	-	0.99	99%
Ondansetron	0.50	50%	0.75	75%	0.02	2%	0.99	99%
Promethazine	0.44	44%	1.0	100%	1.0	100%	0.97	97%
Vitamin K	-	-	0.99	99%	-	-	0.99	99%

Subtitle: S (sensitivity), E (specificity), PPV (positive predictive value) and NPV (negative predictive value)

(-) It was not possible to determine sensitivity and PPV because, according to the researchers' assessment, although the triggers were identified during hospitalisation, they were not related to an ADE.

Source: Authors.

Evolution module trigger prediction accuracy

Trigger sensitivity values and PPVs, which were 0.5–1.0 and 0.05–1.0, respectively, are described in Table 2. The evolution trigger with the best performance was the allergy/allergic reaction/skin rash, pruritus trigger, which had a sensitivity value of 100% and a PPV of 100%. The abrupt interruption of medication trigger followed with a sensitivity value of 100% and a PPV 61%.

Table 2. Accuracy of triggers within the evolution module.

TRIGGER MEDICATIONS	S		E		PPV		NPV	
	n	%	n	%	N	%	n	%
Allergy/allergic reaction/skin rash, itching	1.0	100%	1.00	100%	1.00	100%	1.00	100%
Bradycardia	0.67	67%	0.96	96%	0.22	22%	0.99	99%
Cold	1.00	100%	0.93	93%	0.45	45%	1.00	100%
Diarrhoea/dysentery	1.00	100%	0.95	95%	0.61	61%	1.00	100%
Phlebitis	0.36	36%	1.00	100%	1.00	100%	0.91	91%
Haemorrhage/bleeding /purple/haematoma	1.00	100%	0.97	97%	0.17	17%	1.00	100%
Hyperglycaemia	0.75	75%	0.92	92%	0.39	39%	0.98	98%
Hypoglycaemia	0.50	50%	0.99	99%	0.92	92%	0.93	93%
Hypertension	-	-	0.89	89%	-	-	1.00	100%
Hypotension	0.81	81%	0.94	94%	0.57	57%	0.98	98%
Nausea and/or vomiting	1.00	100%	0.95	95%	0.18	18%	1.00	100%
Excessive sedation, lethargy	1.00	100%	0.94	94%	0.45	45%	1.00	100%
Abrupt discontinuation of medication	1.00	100%	0.91	91%	0.61	61%	1.00	100%
Tachycardia	0.50	50%	0.89	89%	0.05	5%	0.99	99%
Dizziness	-	-	0.98	98%	-	-	1.00	100%

Subtitle: S (sensitivity), E (specificity), PPV (positive predictive value) and NPV (negative predictive value)

(-) It was not possible to determine sensitivity and PPV because, according to the researchers' assessment, although the triggers were identified during hospitalisation, they were not related to an ADE.

Source: Authors.

Laboratory Test module trigger prediction accuracy

The laboratory tests trigger (Table 3) predicted with the greatest degree of accuracy was the increase in creatinine by 0.3 mg/dL (at least two days) trigger, which had a sensitivity value of 67% and a PPV of 59%, while the creatinine 2x above basal had a sensitivity value of 13% and a PPV of 40%.

Table 3. Accuracy of triggers within the laboratory tests module.

TRIGGERS MEDICATIONS	S		E		PPV		NPV	
	n	%	n	%	n	%	n	%
Creatinine 2x above basal level	0.13	13%	0.98	98%	0.40	40%	0.93	93%
Creatinine increase by 50% from baseline (for more than 7 days)	-	-	0.99	99%	-	-	0.93	93%
Increase in Creatinine by 0.3 mg/dL (at least two days)	0.67	67%	0.96	96%	0.59	59%	0.97	97%
Activated partial thromboplastin time (aPTT) > 100 s	-	-	0.99	99%	-	-	0.99	99%
Bilirubin increased 2x, elevated transaminases, without alkaline phosphatase elevation	-	-	0.97	97%	-	-	1.00	100%

Subtitle: S (sensitivity), E (specificity), PPV (positive predictive value) and NPV (negative predictive value)

(-) It was not possible to determine sensitivity and PPV because, according to the researchers' assessment, although the triggers were identified during hospitalisation, they were not related to an ADE.

Source: Authors.

Vital Sign module trigger prediction accuracy

The accuracy analysis of the vital sign trigger is shown in Table 4. Sensitivity varied from 0.24 to 1.0 and the PPV varied from 0.02 to 0.94. The trigger with the best performance was glycaemia > 50 mg/dL (capillary or serum), which had a sensitivity of 68% and a PPV of 94%. And although the trigger glycaemia > 140mg/dL (capillary or serum) had the best sensitivity (93%) among the evolution triggers, its PPV was only 12%.

Table 4. Accuracy of triggers within the vital signs module.

TRIGGERS MEDICATIONS	S		E		PPV		NPV	
	n	%	n	%	n	%	n	%
Blood glucose < 50 mg/dL (capillary or serum)	0.68	68%	0.99	99%	0.94	94%	0.95	95%
Blood glucose > 140 mg/dL (capillary or serum)	0.93	93%	0.32	32%	0.12	12%	0.98	98%
Respiratory rate less than 12 rpm	0.24	24%	0.96	96%	0.36	36%	0.92	92%
Blood pressure < 90/60 mmHg	0.86	86%	0.91	91%	0.44	44%	0.99	99%
Blood pressure < 140/90 mmHg	-	-	0.46	46%	-	-	1.00	100%
Heart rate ≤ 50bpm	1.00	100%	0.93	93%	0.13	13%	1.00	100%
Heart rate >100 bpm	0.50	50%	0.72	72%	0.02	2%	0.99	99%

Subtitle: S (sensitivity), E (specificity), PPV (positive predictive value) and NPV (negative predictive value)

(-) It was not possible to determine sensitivity and PPV because, according to the researchers' assessment, although the triggers were identified during hospitalisation, they were not related to an ADE.

Source: Authors.

Analysis of Trigger Groups

A predictive accuracy analysis of trigger groups is described in Table 5. In this study, an accuracy analysis of triggers revealed that the group of drugs trigger had the highest sensitivity (72%), but lowest PPV (9%). Therefore, the probability of the drug tracker being related to an ADE was determined to be low. The laboratory tests trigger had moderate sensitivity and PPV (62% and 31%, respectively), but had the best specificity (E: 89%) to negative negative predictive value NPV (97%) ratio, meaning that the tracker absence correlated with event absence. However, the evolution tracker had the best ratio between sensitivity (69%) and PPV (68%). Therefore, according to the multidisciplinary team, evolution data were optimal for identifying triggers of ADE.

Table 5. Trigger accuracy based on group classification.

TRIGGER GROUP	S		E		PPV		NPV	
	n	%	n	%	n	%	n	%
Medicines	0.72	72%	0.18	18%	0.09	9%	0.85	85%
Evolution	0.69	69%	0.45	45%	0.68	68%	0.46	46%
Laboratory Exams	0.62	62%	0.89	89%	0.31	31%	0.97	97%
Vital signs	0.67	67%	0.04	4%	0.30	30%	0.15	15%

Subtitle: S (sensitivity), E (specificity), PPV (positive predictive value) and NPV (negative predictive value)

Source: Authors.

In this study, 165 ADE were identified in the 200 patients analysed. The five main ADE identified were as follows: phlebitis (18.1%), hypoglycaemia (16.1%), diarrhoea (10.7%), constipation (8.7%) and hypotension (8.7%). Among the drugs associated with ADE in the present study, the following stand out: insulin (15%), clarithromycin (9%), hydrocortisone (7%), losartan (5%) and piperacillin + tazobactan (5%).

Regarding causality, of 165 identified ADEs, 59% (98) were classified as possible and 36% (59) as probable. Of 165 ADEs, it was not possible to estimate the possibility of preventing their occurrence of 31 (19%) due to data absence, lack of consensus among researchers, or event complexity. Remaining events were classified according to the possibility of preventing their occurrence: 62% (103) were classified as preventable, and 19% (31) as non-preventable as a result of adverse hypersensitivity reactions. When classifying damage, most events were considered mild 119 (72%) due to temporary damage to the patient. The moderate classification corresponded to 26% (43) of cases identified, ADEs in

this category increased the length of the patient's hospital stay. Finally, 3 (2%) events were associated with patient death. One was likely due to a hypersensitivity reaction to iodinated contrast, and the other two were associated with antihypertensive drugs that, due to the severity of the patients' conditions, contributed indirectly to their deaths.

There was no correlation observed between the occurrence of ADE and gender. Variables that best correlated with the occurrence of ADE (> 95% CI), according to Pearson's correlation, were: length of hospitalisation ($r^2 = 0.41$), total drug doses used ($r^2 = 0.33$) and number of active ingredients ($r^2 = 0.30$). A selected linear regression was applied to define factors associated with length of stay. The number of ADEs and the number of active ingredients prescribed were identified, which had r^2 values of 2.78 and 0.55, respectively.

In this study, the difference between the hospital stay length in patients with ADE(s) and those who did not experience an ADE was about 6 days.

4. Discussion

The geriatric patient experiences physiological changes that result from the aging process, and tends to have a greater number of comorbidities associated with acute or chronic health conditions. These characteristics of geriatric patients contribute to their increased risk of hospitalisation (Gon & Kending, 2016. Nunes *et al.*, 2017. Queiroz, Oliveira, Araújo, & Reis, 2016). The national health research in Brazil, states that hospitalisation event is more frequent, with a longer hospital stay and consequently greater cost, in elderly patients (Malta *et al.*, 2017).

In this study, the prevalence of female elderly patients was 53%. Other studies from Rio de Janeiro (Motta, 2002), Belém (Santos, 2007) and Pernambuco (Rodrigues *et al.*, 2017) found that males accounted for 53,5%, 53,1% and 53,8% of hospitalised elderly, respectively. The elevated prevalence of elderly men may have been a result of the gender's increased propensity to neglect their health, their relatively reduced use of child and secondary healthcare services, their elevated risk of clinical decompensation and, consequently, elevated risk of death versus females (Almeida, Mafra, Silva, & Kanso, 2015; Chaimowicz, 2009). In addition, in the present study, 50.6% of the studied hospitalisations involved elderly individuals older than 80 years old, of which 65.9% (66) were females. According to some authors, elderly women have a life expectancy that is 10 years longer than men. This justifies the female predominance regarding individuals hospitalised ≥ 80 years old (Anderson *et al.*, 1998; Robb, Elizabeth, Ashika, & Richard, 2017).

Some authors have correlated ADEs with age, length of stay, female gender and presence of multiple diseases (Rahn, 2008; Robb *et al.*, 2017; Seddon, Cameron, Young, Maharaj, & Miller, 2013). In this study, 60% of patients who had ADE (identified by trigger or not) were female. However, similar to another study developed in Brazil (Almeida *et al.*, 2011), there was no statistical association between ADE and gender.

The average length of hospital stay in this study was determined to be 10 days, which differed from the average duration of hospitalisation of 6 and 16 days, which were reported by Rodrigues *et al* (2017) and Santos (2007) respectively. This difference may be due to an early hospital discharge protocol initiated at the institution where this study was conducted. Since 86% of patients were discharged as a result of clinical improvement, and only 5% were discharged as a result of being completely cured. The early discharge planning scheme implemented by the hospital multidisciplinary team reduced length of hospital stay, iatrogenic occurrence, functional loss, poor outcomes after discharge, hospital readmissions and mortality (Varallo *et al.*, (2017).

Infections were responsible for 41% of hospitalizations, however, in a study carried out by Queiroz *et al.*, (2016) in the ICU of a hospital in Salvador, only 15.5% of hospitalizations were related to infection. The high rate of hospitalisation due to infections found in this study may be a result of the institutionalised sepsis protocol, which facilitates the identification and management of infectious diseases.

Of total reported infections, UTI accounted for 15% of hospitalisations. In elderly patients, UTI are common and typically affect 20% of elderly women and 10% of men. UTI is a major cause of sepsis in hospitalised patients. The high prevalence of UTI in elderly is likely a result of physiological changes, functional and self-care capacity loss, low tolerance to therapeutic procedures, difficulty walking and challenges with use of urinary devices (Silva, Pedreira, Santos, Barros, & David, 2018; Thiago, 2010; Veronese, 2005).

The high occurrence of comorbidities among the elderly (98%), especially systemic arterial hypertension (SAH), Diabetes Mellitus (DM) and Malignant Neoplasm (NM), was also noted by other authors, who both reported a rate of comorbidities in the elderly of 91% (Caldas *et al.*, 2015; Motta, 2002). The high rate of comorbidities observed is also associated with the increased number of drugs used continuously, prescriptions, active ingredients prescribed, and dispensed drugs in elderly individuals, which was also observed in this study. This is reflected in the pharmacotherapeutic risk classification in patients at moderate and high risk for developing drug-related problems, and the almost nonexistent decrease in patient

risk during hospitalisation. This was observed since the number of medications prescribed and age itself were determining factors for scores adopted in the studies.

Regarding triggers, after searching literature databases, it became apparent that most articles did not use the GTT methodology exclusively. Instead, researchers combined the GTT methodology with others and/or triggers to identify triggers with greater specificity. In the present study, triggers occurred in 99.5% of hospitalised elderly patients. Studies in a hospital in the Federal District (Almeida *et al.*, 2001) and another in a tertiary hospital in Rio de Janeiro (Rozenfeld, Giordani, & Coelho, 2013) determined that 9.7% and 70% of the assessed population, respectively, presented a trigger. A study that applied a variation of the GTT methodology and assessed eight US hospitals, determined 87.7% of patients considered had a trigger (Kennerly *et al.*, 2013). In a study carried out in Brazil with elderly admitted to an emergency room, 38 triggers were found in 278 records analysed, eight ADEs were identified. Of the eight adverse reactions described, seven were identified by a trigger (Nagai, Takashi, Pinto, & Romano-Lieber, 2018).

Other studies carried out by Varallo *et al.*, (2017), Cavernalli *et al.*, (2013), Rozenfeld *et al.*, (2013), and Kennerly *et al.*, (2013), determined that 42% , 24%, 22%, 17%, 3%¹ and 2% of triggers were related to ADEs, showing great variability respectively. In this study, 13.7% of trigger occurrences in medical records corresponded to 76% of ADEs identified throughout the period.

The high number of patients who had trigger in this study, and the number of triggers related to ADE, are probably a result of the modification rate of the GTT method proposed by the IHI, which included additional triggers since a study from New Zealand concluded that the rate of GTT tool modification is a determining factor in the ability of the methodology to identify ADE (Seddon *et al.*, 2013). In addition, in retrospective studies, the absence of complete data in medical records has been shown to be a determining factor, as was observed in a study developed in an surgery center, which considered 207 patients. Of the total number of patients considered, 25% did not have complete data in their medical records and 17% did not have available laboratory data. As a result, triggers were associated with only seven ADEs. The authors suggested the need to propose new triggers (Franklin, Birch, Sachter, & Barber, 2010).

Most studies analysed trigger accuracy via exclusively PPV to determine trigger performance. The formula used to evaluate accuracy remains controversial. Some authors consider the occurrence of a tracker per patient, but others consider trigger presence per day. In this study, a low predictive value was associated with the high prevalence of comorbidities

such as SAH and DM, and difficulty establishing a causal relationship between triggers and events occurred due to the clinical complexity of elderly patients.

In this study, the trigger sensitivity varied between 17 and 100% and the PPV varied between 2 and 100%. The PPV was similar to the results of the study by Rozenfeld *et al.*, (2013) and Matlow *et al.*, (2011), who reported values of 12–100% and 0–83.3%, respectively. In the last article trigger analysis was probably not excluded, but no ADE were associated with triggers. In a prospective study conducted in a hospital medical and surgical clinic in Brazil, PPV and NPV were calculated according to days on which the triggers occurred. In the study, trigger sensitivity ranged from 0.3 to 11.8% and PPV ranged from 1.2 to 27.3%, while specificity and NPV were greater than 86% (Silva, 2017). Values below those found in this study were also observed in a different study in which PPV varied between 0–0,67% (Carnevalli, *et al.*, 2013).

Regarding drug triggers, hydrocortisone, diphenhydramine and fexofenadine have been reported to be the best triggers, with sensitivity values of 57%, 14% and 14%, respectively (Almeida *et al.*, 2011). Variation between studies can occur, due to service profile itself, and protocols for medicine use established throughout study sites.

The trigger creatinine increase by 50% from baseline (for more than 7 days) was associated with kidney damage, there was only one occurrence of the tracker, which was not related to an ADE but instead to pre-existing kidney damage. The low occurrence of the tracker may be associated with the 7-day period needed to define the trigger. In the 44% (88) of patients who had a hospital stay of less than 7 days, it was not possible to identify the trigger. Further, it must be considered that the creatinine baseline does not always occur on the first day of hospitalisation.

In this study, although glycaemia > 50mg/dL (capillary or serum) and the progress tracker hypoglycaemia (sensitivity, 50%; PPV, 92%) performed well, mistakes related to filling out vital sign data in the patient's electronic medical record were observed, and despite blood glucose records appearing to be greater than 70mg/dL in the system, when investigated, 50% glucose was dispensed and administered to 100% of the patients who presented with hypoglycaemia. Thus, when we analysed factors that contributed to the events, all were preventable by performing simple measures such as insulin administration, training, and maintaining compliance with protocols for safe use of medicines that were already instituted within hospitals. These data are in accordance with findings reported by another study that evaluated the occurrence of ADE in which 19% (8) of the events hypoglycaemic events were associated with incorrect infusion practices (administration of an incorrect volume of insulin),

and two cases of abuse by hypoglycaemic events were classified as preventable (Nilsson, Pih, Tagsjo, & Ericsson, 2012).

The performance of each tracker should be analysed in order to identify the best trigger for ADEs in a particular context and, possibly, subsidise the creation of a tool adapted to carry out pharmacovigilance. The number of ADEs found in this study (165) was similar to the number Passarelli (2005) identified in a study that involved 186 hospitalised elderly patients and identified 199 ADE. Another study that also evaluated the use of GTT in a hospital in Brazil identified hypotension and constipation as principal adverse events, and the ADEs were responsible for 21.2 and 18.3% of all identified ADEs, respectively (Silva, 2017).

The recommendation of the Infusion Nurses Society is that phlebitis occurs at a rate >5%. The incidence of this ADE may vary according to its means of identification (medical records, active search, spontaneous notification), or protocols for the infusion of drugs established at relevant institutions (Infusion Nurses Society, 2006). In this study, of the 30 total phlebitis cases observed, 60% were not identified by the phlebitis evolution tracker, since the event was not described in the medical records and was identified via a bedside pharmaceutical visit and/or via the questioning of health professionals involved in patient care. Of the total phlebitis events, 11 were related to medication errors such as incorrect dilution or incorrect infusion time, even though pharmacists evaluated all prescriptions prior to their use, and the system used at the hospital already included information regarding suitable dilutions and infusion times to guide the prescriber. However, some prescribers changed information manually and, in other cases, medications was prescribed correctly, but their dilution, reconstitution and infusion time were incorrectly carried out by the nursing staff.

Further, as the study progressed, an association between contusion gel dispensing and the occurrence of ADE was observed. When we analysed medication dispensed, 29 patients (96.2%) used the gel, which was a possible tracker of phlebitis within the institution, and had an advantage of dispensal data being available in the pharmacy sector. The ADEs found, including phlebitis, were mostly associated with the use of antimicrobials. These results are in accordance with other studies, which also reported anti-infectives (Almeida *et al.*, 2011), antidiabetics (Shehab *et al.*, 2016) and cardiovascular agents (Rozenfeld *et al.*, 2013) as main causes of ADE. Regarding causality, in accordance with this work, a prior study revealed that 71% of ADE were classified as possible and 29% were classified as probable (Almeida *et al.*, 2011). A systematic review with meta-analysis by Hakkarainen (2012), which evaluated

preventability, revealed that at least half of all ADEs were preventable. This was in accordance with findings reported here, which showed that 62% of events were preventable.

In the Rozenfeld *et al.*, (2013) study, of the total of adverse events identified, 82% contributed to or caused temporary damage requiring intervention, and 6.0% may have contributed to the death of patients. Rozich, Haraden & Resar (2003) reported that 79.9% (219) of events resulted in temporary damage to patients, value close to that which was in this work, and 2% of the events were associated with patient death.

The presence of a comorbidity (13%), number of active ingredients used (30%) and total number of dispensed drugs (33%) were associated with ADE occurrence. This is in accordance with published findings that reported that polytherapy, and comorbidities were factors related to ADEs¹. Multiple linear regression identified comorbidities, number of active ingredients and number of ADEs as factors responsible for 56% of hospital stay duration variation. In isolation, the occurrence of an ADE was responsible for 41% of hospital stay variation. Rozenfeld *et al.*, (2013) established that the length of hospital stays for patients with ADE was, on average, 35 days, and 11 days for patients without ADEs. The patient's length of hospital stay is associated with an increased risk of care events and an elevated cost of health services.

Limitations of this study include the authors' interpretation of the possibility of the prevention of an event, since the line between what is avoidable and unavoidable is subtle and sometimes subjective (Nilsson *et al.*, 2012). We also highlight the quality of the electronic record used. Even as a prospective study, it was possible to identify flaws regarding filling out patient data. In addition, patients are continually monitored by clinical pharmacists at the hospital, and this study did not estimate the number of ADEs that were prevented by these professionals.

5. Conclusions

The trigger tool proved to be effective for identifying ADEs. The performance was similar to that which was reported by other authors who estimated that triggers can be used to identify up to 20 times more events. In fact, only seven events were noted by the multiprofessional team during the study period. The best performing triggers were medication (diphenhydramine and promethazine); evolution (allergy/allergic reaction/skin rash, pruritus; hypoglycaemia; abrupt stop of medication); laboratory tests (increase of creatinine by 0.3 mg/dL); vital signs (blood glucose < 50mg/dL (capillary or serum), blood pressure <

90/60mmHg), dispensal of medication for contusion, and 50% glucose (if necessary). Event identification and the analysis of its cause is necessary to characterize health programmes and to identify failures in health care and follow through indicators, and improve protocols that are implemented to promote the safety of care, and the rational and safe use of medicines. All events identified in this survey were reported to the hospital's risk management department so that individual analyses of each event using the London Protocol could be performed.

Data availability statement

Data that support the findings of this study are available from the corresponding author upon request. The data are not publicly available due to privacy and/or ethical restrictions.

References

Almeida, A. V., Mafra, S. C., Silva, E. P., & Kanso, S. (2015). The feminization of old age: a focus on the socioeconomic, personal and family characteristics of the elderly and the social risk. *Textos & Contextos*, 14 (1), 115-31.

Almeida, M. R., Castro, L. L. C., & Caldas, E. D. (2011). Conhecimentos, práticas e percepção de risco do uso de medicamentos no Distrito Federal. *Rev Ciênc Farm Básica Apl*; 32(1), 225-232.

Almeida, S. M., Romuado, A., Ferraresil, A. A., Zelezoglol, G. R. Z., Marra, A. R., & Edmond, M. B. (2017). Use of a trigger tool to detect adverse drug reactions in an emergency department. *BMC Pharmacol Toxicol*, 18(71), 1-7.

Anderson, M. I. P., Assis, M., Pacheco, L. C., Silva, E. A. S., Menezes, I. S., Duarte, T., Storino, F. M., & Motta, L. (1998). Saúde e qualidade de vida na terceira idade. *Textos sobre envelhecimento*, 1(1), 23-43.

Balderas, V. et al. (2011) the hematocrit level in upper gastrointestinal hemorrhage: safety of endoscopy and outcomes. *Am J Med*, 124(10), 970-6.

Caldas, C. P., Veras, R. P., Motta, L. B., Guerra, A. C. L. C., & Carlos, M. J., Trocado, C. V. M. (2015). Atendimento de emergências e suas interfaces: o cuidado de curta duração a idosos. *Bras Econ Saúde*, 7(1), 629.

Carnevalli, L., Krug, B., Amant, F., Pee, D. V., Gérard, V., Béthune, X., & Spinewine, A. (2013). Performance of the Adverse Drug Event Trigger Tool and the Global Trigger Tool for Identifying Adverse Drug Events: Experience in a Belgian Hospital. *Ann Pharmacother*, 47(11), 1414– 1419.

Carvalho, M. F. C., Romano-Lieber, N. S., Bergsten-Mendes, G., Secoli, S. R., Ribeiro, E., Lebrão, M. L., & Duarte, Y. A. O. (2012). Polifarmácia entre idosos do Município de São Paulo - Estudo SABE. *Rev Bras Epidemiol*, 15(4), 817-27.

Chaimowicz, F. (2009). Dementia in the Brazilian population: prevalence estimates for 2010-2050. *Dement Neuropsychol*. 3(2),169-170.

Charles, V. (2010). *Segurança do paciente: orientações para evitar os eventos adversos*. Porto Alegre (RS), Brasil.

Classen, D. C., Pestotnik, S. L., Evans, R. S., & Burker, J. P. (1991). Computerized surveillance of adverse drug events in hospital patients. *JAMA*, 266(20), 2847-51.

Davies, E. C., Green, C. F., Mottram, D. R., & Pirmohamed, M. (2006). Adverse drug reactions in hospital in-patients: a pilot study. *J Clin Pharm Ther*, 31(4), 335-41.

Farthing, M., et al. (2013). Acute diarrhea in adults and children: a global perspective. *J Clin Gastroenterol*, 47(1), 12-20.

Franklin, B. D., Birch, S., Sachter, M., & Barber, N. (2010). Testing a trigger tool as a method of detecting harm from medication errors in a UK hospital: a pilot study. *Int J Pharm Pract*, 18(5), 305-11.

Gomes, V. P., Silva, M. T., & Galvão, T. F. (2017). Prevalência do consumo de medicamentos em adultos brasileiros: uma revisão sistemática. *Ciênc. saúde colet.* 22 (8), 2615-2626.

Gong, C. H., & Kending, H. (2016). Factors predicting health services use among older people in China: An analysis of the China Health and Retirement Longitudinal Study 2013. *BMC Health Serv Res*; 16(1), 63.

Griffin, F. A., & Resar, R. K. (2009). *IHI Global Trigger Tool for Measuring Adverse Events (Second Edition)*. Innovation Series white paper. Cambridge, Massachusetts: Institute for Healthcare Improvement.

Hakkarainen, K. M., Hedna, K., Petzold, M., & Hagg, S. (2012). Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions: a meta-analysis. *PLoS One*, 7(3), 33236.

Iannini, P. et al. (2006). Adverse cutaneous reactions and drugs: a focus on antimicrobials. *J Chemother*, 18(2), 127-39.

Infusion Nurses Society. (2006). Infusion nursing standards of practice. *J Infus Nurs*, 29(1), S1-92

Kennerly, D. A., Saldaña, M., Kudyakov, R., Graca, B., Nicewander, D., & Compton, J. (2013). Description and Evaluation of Adaptations to the Global Trigger Tool to Enhance Value to Adverse Event Reduction Efforts, *J Patient Saf*, 9(2), 87-95.

Lindberg, G. et al. World gastroenterology Organisation Global Guideline: Constipation a global perspective. *J Clin Gastroenterol*, 45(6), 483-7.

Makary, M. A., Daniel, M. (2016). Medical error—the third leading cause of death in the US. *BMJ*; 353.

Malta, D. C., Bernal, R. T. I., Lima, M. G., Araújo, S. S. C., Silva, M. M. A., Freitas, M. I. F., & Barros, M. B. A. (2017). Doenças crônicas não transmissíveis e a utilização de serviços de saúde: análise da Pesquisa Nacional de Saúde no Brasil. *Rev Saúde Pública*, 51(1), 1-10.

Matlow, A. G., Cronin, C. M. G., Nijssen-Jordan, V. F. C., Fleming, M., Brady-Fryer, B. H. M. A., Orbine, E., Flintoft, V., Hiltz, M. A., & Baker, G. R. (2011). Description of the development and validation of the Canadian Paediatric Trigger Tool. *BMJ Qual Saf*, 20(5), 416-423.

Mendes, W., Martins, M., Rozenfeld, S., & Travassos, C. (2009). The assessment of adverse events in hospitals in Brazil. *Int J Qual Health Care.*, 21(4), 279-84.

Motta, L. B. (2002). Levantamento do perfil de idosos internados em um hospital geral: análise do processo de internação frente às demandas da população geriátrica. *Textos Envelhecimento*; 3(6).

Nagai, K. L., Takashi, P. S. K., Pinto, L. M. O., & Romano-Lieber, N. S. (2018). Uso de rastreadores para busca de reações adversas a medicamentos como motivo de admissão de idosos em pronto-socorro. *Ciência & Saúde Coletiva*, 23(11), 3997-4006.

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Domecq, C., & Greenblatt, D.J. (1981). A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther*; 30(2), 239-245.

Nephrology, I. S. O. (2012). KDIGO *Clinical Practice Guideline for Acute Kidney Injury*. Kidney international supplements.2.

Nilsson, L., Pih, A., Tagsjo, M., & Ericsson, E. (2012). Adverse events are common on the intensive care unit: results from a structured record review. *Acta Anaesthesiol Scand*, 56(8), 959-965.

Nunes, B. P., Uhlmann, M., LI, S., Wachs, L. S., Volz, P. M., Saes, M. O., Duroi, S. M. S., ThúmeI, E., & Facchini, L. A. (2017) Hospitalização em idosos: associação com multimorbidade, atenção básica e plano de saúde. *Rev Saúde Pública*; 51(1), 1-10.

OMS - Organização Mundial da Saúde. (2002). *Safety monitoring of medicinal products. The importance of pharmacovigilance*. Genebra: Organización Mundial de la Salud.

OMS - Organização Mundial da Saúde. (2017). *Medication Without Harm - Global Patient Safety Challenge on Medication Safety*. Geneva: World Health Organization.

Paliativos, A. B. D. C. (2011). Concenso Brasileiro de Náuseas e Vômitos em Cuidados Paliativos. *Revista Brasileira de Cuidados Paliativos*, 3(3), 2.

Passarelli, M. C. G. (2005). *Reação Adversa a medicamentos em uma população idosa hospitalizada*. Tese, USP, São Paulo, Brasil.

Pastore, C. et al. (2009). Diretrizes da Sociedade Brasileira de Cardiologia sobre Análise e Emissão de Laudos Eletrocardiográficos. *Arquivos Brasileiros de Cardiologia*, 93,1-19.

Pizzol, T. S. D., Pons, E. S., Hugo, F. N., Bozzetti, M. C., Sousa, M. L. R, & Hilgert, J. B. (2012). Uso de medicamentos entre idosos residentes em áreas urbanas e rurais de município no Sul do Brasil: um estudo de base populacional. *Cad. Saúde Pública*, 28(1),104-114.

Potter, P. A., & Perry A. G. (2013). Fundamentos da Enfermagem. Rio de Janeiro: Elsevier,29, 458-504.

Queiroz, D. B., Oliveira, L. C., Araújo, C. M., & Reis, L. A. (2016). Perfil de internações de idosos em uma clínica de neurociências de um hospital público. *Rev Enferm Contem.*, 5(1), 16-24.

Rahn, D. D. (2008). Urinary Tract Infections: Contemporary Management. *Urologic Nursing*, 28(5), 333-340.

Robb, G., Elizabeth, L. O. E., Ashika, M., & Richard, H. M. S. (2017). Medicationrelated patient harm in New Zealand hospitals. *NZ Med J*, 130(1460), 21-32.

Rodrigues, C. C., Ribeiro, R. C. H. M., Cesarino, C. B., Bernardi, C., Bertolin, D. C., Ribeiro, R. M., Oliveira, M. P., Kusumota, L., & Jorge, S. C. (2017). Idosos Internados em um Hospital Escola: Característica Clínicas e desfechos. *Rev enferm UFPE online*, 11(12), 4938-45.

Rozenfeld, S., Giordani, F., & Coelho, S. (2013). Eventos adversos a medicamentos em hospital terciário: estudo piloto com rastreadores. *Rev. Saúde Públ.*, 47(6), 1102-1111.

Rozich, J. D., Haraden, C. R., & Resar, R. K. (2003). Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care*, 12(3), 194-200.

Santos, M. I. P. O. (2007). Perfil dos idosos internados no Hospital Geral em Belém (Pará) *Esc Anna Nery R Enferm.*, 11(1), 23-9.

Seddon, A. J., Cameron, C., Young, M. L., Maharaj, L. E. A. M., & Miller, N. (2013). The Adverse Drug Event Collaborative: a joint venture to measure medication-related patient harm. *NZ Med J*; 126(1368), 9-10.

Shehab, N., Lovegrove, M. C., Geller, A. I., Rose, K. O., Weidle, N. J., & Budnitz, D. S. (2016). US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*, 316 (20), 2115–2125.

Silva, A. L., Ribeiro, A. Q., Klein, C. H., & Acurcio, F. A. (2012). Utilização de medicamentos por idosos brasileiros, de acordo com a faixa etária: um inquérito postal. *Cad. Saúde Pública*; 28(6),1033-1045.

Silva, J. B. V. B., Pedreira, L. C., Santos, J. L. P., Barros, C. S. M. A., & David, R. A. R. (2018). Perfil clínico de longevos em uma unidade de terapia intensiva. *Acta Paul Enferm*, 31(1): 39-45.

Silva, M. D. G. (2017). *Avaliação da acurácia dos rastreadores propostos pelo Institute for Health Care Improvement para identificação de eventos adversos a medicamentos*. Tese Doutorado, Universidade Federal de Minas Gerais. Faculdade de Medicina, Minas Gerais,

Brasil. Recuperado de: http://www.bibliotecadigital.ufmg.br/dspace/bitstream/handle/1843/BUOSAQARDW/md_tese__2017.03.21_.pdf?sequence=1>

Sobrafo, S. B. D. F. E. O., & Anvisa, A. N. D. V. S. (2011). *Guia para Notificação de Reações Adversas em oncologia*. São Paulo: Conectfarma publicações científicas.

Sociedade Brasileira de Diabetes. (2015). *Diretrizes da Sociedade Brasileira de Diabetes*. 2015-2016. Rio de Janeiro, Brasil.

Temple, R. (2006). Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf*, 15(4), 214-3.

Thiago, M. R. (2010). *Como diagnosticar e tratar infecção urinária*. Ed. Moreira JR, São Paulo, Brasil.

Varallo, F. R., Hernandez-Dagli, C., Pagottoz, C., Nadai, T. R., Herdeiro, M. T., & Mastroianni, P. C. (2017). Confounding Variables and the Performance of Triggers in Detecting Unreported Adverse Drug Reactions. *Clin Ther*, 39(4), 686-696.

Veronese, R. F. (2005). *Tratado de infectologia*. (3a ed.), São Paulo: Atheneu.

VII *Diretrizes Brasileiras de Hipertensão*. (2016). Arquivos Brasileiros de cardiologia. 95, I-III.

Percentage of contribution of each author in the manuscript

Christicia Jamilly Pinto de Sousa – 40%

Ana Cristina Lo Prete – 30%

Carolina Heitmann Mares Azevedo Ribeiro – 30%