International Classification of Diseases Codes as screeners for Adverse Drug Events

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ABSTRACT

Introduction: Adverse drug events (ADEs) represent health risks and their underreporting represents a challenge to public health. The active search for suspected cases of ADE in health databases using the International Classification of Diseases-CID is one of the strategies that can reduce underreporting of these events. **Objective:** The aim of this study is to identify the ICD codes most commonly used as tracers of ADE and to assess their concordance among researchers. **Methods:** A systematic literature review was conducted using the PubMed, Scopus, Web of Science, MEDLINE and LILACS databases with the descriptors "International Classification of Diseases", "ICD-10", "Drug-Related Side Effects and Adverse Reactions", "Poisoning", "Medication Errors". The included articles had their ICD codes identified, compared and their quality assessed. The analysis of concordance of the codes was done using Bernoulli's test model, exact binomial proportions tests and the false discovery rate technique to analyze the hypotheses posed. Statistical analysis was done using R software. The study is registered in PROSPERO under CRD42019120694. **Results:** A total of 5,167 articles were identified and after the selection criteria, 33 were included in this review. A total of 1,105 ICD codes were identified. The prevalence coefficient of ADEs ranged from 0.18% to 18.4% in hospital admissions and the mortality rate ranged from 0.12 to 45.9 deaths per 100,000 deaths. Only 195 (17.7%) codes had high concordance among researchers. Many ICD codes used to detect ADEs have low inter-rater concordance and produced different event rates. **Conclusion:** The identified ADE tracking codes represent a simple and efficient method for capturing adverse events in large healthcare databases, contributing to the reduction of underreporting in traditional ADE reporting systems.

Keywords: Medical informatics, Pharmacoepidemiology, Patient safety, International classification of diseases, Drug-related side effects and adverse reactions.

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INTRODUCTION

It is undeniable that the pharmacological therapeutic arsenal has contributed to reducing morbidity and mortality, and improving the quality and life expectancy of populations. However, adverse drug events (ADEs) can damage health, determine or prolong hospital stays, and eventually cause death,[1-3] especially in children[1] and the elderly.[2-4] In Western countries, ADEs account for 3-6% of all hospital admissions,[3,5] determine major economic implications, characterizing as an important public health problem.[1,3,6]

The activities related to pharmacovigilance include in its scope the surveillance of ADEs, mainly through spontaneous notification[1,6]. As a passive surveillance method, it has as some of its advantages the high coverage potential and a good cost-effectiveness ratio[7]. However, it presents an important limitation, which is the underreporting, which can be higher than 90%[6,8]. To overcome this challenge, different methods of active surveillance have been used, such as reviewing medical records, interviewing patients, reviewing structured charts, data mining to detect "signs" and active search using codes from the International Classification of Diseases - ICD.[6]

The use of the active surveillance method, in general, is more expensive, requires better infrastructure in health services and more training of professionals to execute it[2], however, the use of ICD codes has demonstrated efficacy, simplicity and low cost in the identification of ADEs[7,8], due to their suitability for health information and the increasing use of these codes in health systems to classify diagnosis, service utilization and death data[9].

The use of ICD codes to track ADE has been tested in other countries[2,4,7,8] and recently in Brazil[9-11]. However, the set of ICDs used varies widely among authors, greatly impacting the estimates of ADE prevalence depending on the list used[4,8]. Thus, this study aims to identify the ICD-10 codes most commonly used in the literature as tracers of ADE and to present them according to the degree of concordance among primary studies.

METHODS

This is a systematic literature review, registered in PROSPERO[12] No. CRD42019120694 and protocol available at https://www.crd.york.ac.uk/PROSPERO/. This study follows the PRISMA reporting guidelines[13].

ADE is any unfavorable medical occurrence that may occur during treatment with a drug, but is not necessarily causally related to that treatment[6]. This definition has made it possible to study events potentially associated with medications, including adverse drug reactions (ADRs), medication errors, poisoning, and medication abuse.

For clarity, delimitation in the search and direction during the literature search strategies, the tool designated by the acronym PICO[14] was used to formulate the following starting question: what are the main ICD codes used as trackers of Adverse Drug Events in health information systems? (chart1)

The literature search was conducted in the electronic databases Pubmed, Scorpus, Web of Sciences, MEDLINE, and LILACS. In addition, manual searches were performed in the bibliographic references of articles, in the Brazilian database of theses and dissertations (BDTD), and in Google Scholar. For the gray literature search, Google was used. The structured vocabularies DeCS-Health Sciences Descriptors and in the English bases the Medical Headings (MeSH) dictionary terms were used. Both DeCS and MeSH were combined using Boolean terminology ("AND", "OR" and "AND NOT"). During 2019, journal scans were conducted, and no other articles of interest were identified. (Chart 2).

Duplicate publications were removed with Dupli find software[15]. One researcher (RM) reviewed all titles and identified potential article eligibility. In addition, review of the abstracts of eligible papers and application of the inclusion and exclusion criteria were performed by a pair of researchers (RM and EV). Thus, the reading of the abstracts was not blinded to authorship or journal. With this, the primary studies were evaluated by two authors with experience in pharmacovigilance. Finally, disagreements about study eligibility were resolved by consensus among the authors and the Kappa.

Articles that used ICD-10 to track ADE in patients and that presented the list of codes used in the study were included. Studies published only as abstracts were excluded, i.e., those that contained insufficient information about the data sources and/or the definition of ADE adopted or studies that used only one ICD code, such as those specific to studies with benzodiazepines (ICD Y47.1). In addition,

articles that used an ICD list already published by other authors were also ineligible.

The data was extracted with a standardized form in an Excel® spreadsheet. Disagreements were resolved by consensus or by a third-party reviewer (PA), if necessary. These data included the characteristics of the studies (design, country, main objective, data source, methods applied).

Due to the inexistence of an instrument considered adequate for assessing quality and bias in observational studies,[16] an instrument was created with some criteria derived from three commonly used instruments (Chart 1): GRADE[17] System, York Center[18] and Loney Criteria[19].

Chart 1 PICO Strategy Description.

Acronym	Definition	Description
P	Problem	Multiple lists with ICD codes with different ADE rates.
I	Intervention	Use of ICD codes in the Health Information System
C	Comparisson	Compare the inclusion or not of each code in the researchers' lists.
O	Results	Available list of researcher codes, ADE prevalence rate.

The ICD-10 codes identified in the selected studies were organized in an Excel® spreadsheet and classified according to the nature of the ADE to which they belonged, aggregated into six categories: i) adverse drug reaction-ADR; ii) intoxications, iii) medication errors, iv) other adverse events not classified elsewhere (AE-NCOP), v) personal history of drug allergies and vi) drug abuse. They were then coded as follows: they received the number "1" if the author studied the nature of ADE and included the ICD-10 code; they received "0" (zero) if the author studied the class of ADE and did not include the code that was already part of another included list; and finally, they received "9" if the author did not include the code because it did not belong to the class of ADE of his study, i.e., the absence of that code will not interfere in the concordance.

The methods of code selection in the studies were classified as direct and mixed. In the direct method, the codes that had in their description the words "medication" or "drug" were selected, therefore, they signaled injuries 100% attributable to the use of medications or drugs. The mixed method used, in addition to the direct method, other codes that the scientific literature and/or clinical experience indicated were related to ADE, such as the code L51.1- Stevens-Johnson Syndrome. Therefore, these are codes that have some probability of being attributable to the use of medication or drugs.

The variable "concordance" quantifies the degree of acceptance of each ICD code among the studies. Sample concordances (set of selected studies) were used to estimate population concordance. One-sided hypothesis tests were constructed in order to verify if a given code has minimally enough concordance to be included in the consensus list.

Given that X_i is a binary random variable such that $[X_i = 0]$ and $[X_i = 1]$ are values associated with the events "ICD_i was not used" or "ICD_i was used" respectively and that the authors' opinions are considered independent of each other, it is assumed that X_i follows Bernoulli with probabilities $P[X_i = 1] = p_i$ and $P[X_i = 0] = 1 - p_i$.

Consider that $X_{i1}, \ldots, X_{ini}$, independent trials and that the probabilities of "success" are identical for each trial, associated with the use of ICD_i by the n_i authors. The random variable $Y_i = \sum_{-}(j = 1)\hat{}(ni)X_{ij}$, follows the Binomial model with parameters n_i and p_i, denoted by Yi ~ B(ni, pi), whose probability function is given by

$$P[Y_i = y] = \frac{n_i!}{y!(n_i - y)!} p^y{}_i (1 - p_i)^{n_i - y} I_{\{0,1,\ldots\}}(y).$$

Finally, the population concordances for each ICD code, represented in the binomial models by the p_i parameters, were estimated by means of the relative frequencies of each ICD code. The consensus lists were composed of codes with concordance greater than a cutoff point. Being c some order statistic: first, second or third quartile of the observed concordances. To evaluate if each p_i is significantly higher than c, the exact binomial proportions test was adopted, given by

$$H0: p\_(i) \leq c,$$

$$H1: p\_i > c; \text{ em que } i = 1; \ldots; 1105.$$

To control the number of wrongly rejected hypotheses, the false discovery rate (fdr) [20] technique was used. R software was used for the statistical analysis. The functions binom.test and p.adjust, both contained in the stats package[21]. Fdr equal to 0.20

Chart 2 Search strategies used in the literature search.

Search strategies used	
Search Base	**Search Strategies**
PubMed	((((((“international classification of diseases”[MeSH Terms] OR (“international”[All Fields] AND “classification”[All Fields] AND “diseases”[All Fields]) OR “international classification of diseases”[All Fields]) OR ICD[All Fields]) AND ((“information storage and retrieval”[MeSH Terms] OR (“information”[All Fields] AND “storage”[All Fields] AND “retrieval”[All Fields]) OR “information storage and retrieval”[All Fields]) AND (“methods”[Subheading] OR “methods”[All Fields] OR “methods”[MeSH Terms]))) AND (Drug-related[All Fields] AND problems[All Fields])) OR (“drug-related side effects and adverse reactions”[MeSH Terms] OR (“drug-related”[All Fields] AND “side”[All Fields] AND “effects”[All Fields] AND “adverse”[All Fields] AND “reactions”[All Fields]) OR “drug-related side effects and adverse reactions”[All Fields] OR (“drug”[All Fields] AND “related”[All Fields] AND “side”[All Fields] AND “effects”[All Fields] AND “adverse”[All Fields] AND “reactions”[All Fields]) OR “drug related side effects and adverse reactions”[All Fields])) AND (“poisoning”[Subheading] OR “poisoning”[All Fields] OR “poisoning”[MeSH Terms])) AND (“medication errors”[MeSH Terms] OR (“medication”[All Fields] AND “errors”[All Fields]) OR “medication errors”[All Fields] OR (“errors”[All Fields] AND “medication”[All Fields]) OR “errors, medication”[All Fields])
Scopus	international classification of diseases OR ICD AND drug-related side effects and adverse reactions OR poisoning OR medication errors
Web of Science	TS=(“international classification of diseases” OR “ICD” AND “drug-related side effects and adverse reactions” OR “poisoning” OR medication errors AND Drug-related problems) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=1980-2018
LILACS	International Classification of Diseases [Subject descriptor] and Medication-Related Side Effects and Adverse Reactions [Subject descriptor] or Poisoning [Subject descriptor] or Medication errors [Subject descriptor]
Medline EBSCO	international classification of diseases OR ICD codes AND (drug-related side effects and adverse reactions ”[Mesh]) OR medication errors or drug errors) AND (information storage and retrieval system)
Google Acadêmico	(tw:("International Classification of Diseases") and tw:(Drug-Related Side Effects and Adverse Reactions))
BDTD	"(Subject:Adverse drug reactions OR Subject:International Classification of Diseases OR Subject:Poisoning)"

was chosen, that is, a maximum of 20% of the null hypotheses were wrongly rejected.

To classify each ICD according to the degree of concordance, a new variable “degree” was defined with values: 0 - Insufficient, 1 - Low, 2 - Median and 3-High. For each ICD three hypothesis tests are performed, if p_i is significantly higher than the first, second or third quartile of the concordances, this code will have grade 1 (low concordance), 2

(Median) or 3 (high) respectively, otherwise grade 0 (insufficient concordance).

Ethics committee approval of the study was not necessary because it did not involve human subjects or medical records with the identification of persons.

RESULTS

A total of 5,167 articles were retrieved, of which 1,410 were excluded for being duplicates. After applying the established eligibility criteria, 33 articles were included (Figure 1). Good inter-reviewer reproducibility was observed in the screening stages, with Kappa (κ)= 0.71. A total of 1,105 ICD-10 codes were identified, with a range of 1297 to 79622 codes in the primary studies. The studies of ADEs in general averaged 377 codes with standard deviation (SD) = 134, those unique to ADRs averaged 346 codes (SD = 167.6), and studies to identify cases of poisoning averaged 340 codes (SD = 92.3).

Among the total codes studied (n=1,105), 176 (15.9%) were part of chapter 19 (injuries, poisoning and other consequences of external causes) and 383 (34.7%) of chapter XX (External causes of morbidity and mortality). The remaining 546 codes (49.4%) were divided into the other ICD chapters and represent disease manifestation codes. Of the total codes identified, 700 (63.3%) had in their code description the words "medicines", "drugs" or name of the therapeutic class of the drug causing the adverse event.

Regarding the nature of the codes, 722 codes (65.3%) were classified as ADR trackers, distributed as follows: 491 (68.0%) ADR-disease manifestations, 53 (7.3%) ADR-signs and symptoms, and 178 (24.6%) ADR-external causes. Another 332 codes (30.0%) such as trackers for poisoning, 22 (2.0%) other AE-NCOP, 11 (1.0%) for medication error, 11 (1.0%) for personal history of allergies and 7 (0.6%) for drug abuse.

As for the place of origin of the selected studies, eleven (33.3%) were conducted in Europe[2,4,7,23-30], eight (24.2%) in Oceania[2,22,31-36], seven (21.2%) in North America[37-43], six (18.2%) in South America[9-11,44-46] and one (3.0%) in Asia[47]. The countries with the largest number of studies were Australia (n=7), Brazil (n=6) and England (n=6). As for the main outcome, 15 (45.4%) studies evaluated ADE (in general)[9,11,24,25,31,33,38-40,46-51], 14 (42.4%) evaluated only ADR[1,2,7,22,23,26-30,35,36,44,51] and 4 (12.1%) specifically drug intoxications[10,40-42] (Chart 3).

Most studies used a cross-sectional design[1,2,7,9-11,22,23,25-31,36,37,41-44,47,49] (87,8%). Hospital administrative data was the most explored source in the studies (75.7%)[2,7,9,22,24-26,28-30,32,33,35,36,38,40,43,44,47,50,51], then the mortality data (24.4%)[10,22,23,31,40,42,47], pharmacovigilance data (15.1%)[7,28,32,33,37], and primary or outpatient care (6.0%)[43] (Chart 3).

The proportion of hospitalizations caused by ADE in the general population ranged from <1%[9,11,29,32] to 8.3%[25] of hospitalizations, while in mortality from 0.1%[36] to 1.07%[40]. In studies with unique ADR codes, the proportion of hospitalizations ranged from <0.5% in hospitalizations[26,27] up to about 3%[28], except in the study of elderly rehospitalizations in Australia that showed a prevalence of 18.4%[35]. Regarding ADR deaths, only the study by Shepherd et al, used these codes to exclusively explore mortality trends, where a rate of 0.12 ADR deaths per 100,000 deaths was estimated in the US[43]. For poisoning, all the retrieved studies had death as the outcome. [10,40–42] A study conducted in the US estimated a poisoning death rate of 5.0 and 7.8 per 100,000 all-cause deaths[40]. In Brazil a study identified 45.9 deaths from drug intoxication per 100,000 deaths[10] (Chart 3).

Overall, thirteen studies (39.3%) used the direct method to identify the codes of interest[1,10,26,33-36,40-43,46-48], while fifteen studies (45.5%) used a mixed method[2,4,9,11,22,23,25,27,29,31,32,37-39,49]. In five studies (6.1%) the method of ICD code selection was not identified[7,24,28,30,45].

Table 4 shows the results of the quality analysis of the 33 articles included in the review by each selected criterion. Of the total, 29 articles (87.8%) were considered to be of good quality for study design, sampling method and sample size (criterion 1). In 15 studies (45.4%) the authors detailed the method of selection of their ICD codes, while in the others (54.6%) it was not clear in the text, the method of selection of the codes used (criterion 2).

Most studies (n=28, 84.8%) presented preventive measures to minimize biases and errors in sample selection (criterion 3) and were describing the subjects in detail, similar to routine practice where the intervention can be implemented (criterion 4). The others did not make clear the use of strategies to minimize these problems. Among all studies, 21 (63.6%) reported that the primary outcome was defined explicitly by the

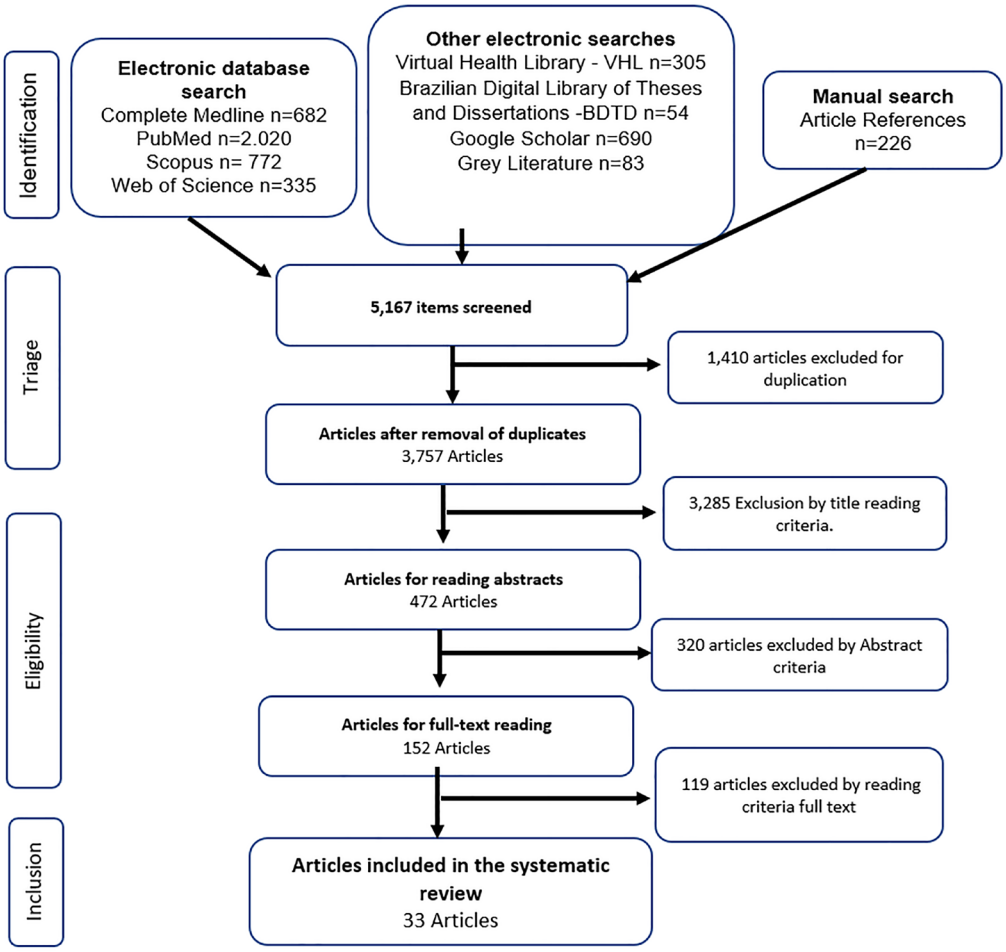

Figure 1 Search flow and selection of articles from the systematic review.

description of the word "medication/drugs" in the text description of the ICD codes, and in the others (n=12, 36.4%), the primary outcome measures were selected independent of the ICD-10 code set (criterion 5).

Only five studies (15.1%) estimated the sensitivity and/or specificity of their set of ICD codes. Parameswaran Nair et al[1] compared the estimation of ADR identification by the "Y40-Y59.9" codes with the prospective identification of ADR by pharmacists. The authors demonstrated that ADE detection with these codes was much lower than the prospective data collection method. Hohl et a[37] compared the number of ADEs diagnosed and recorded at the point of care with those recorded in administrative data and their code list showed a sensitivity of 28.1%. Reynolds et al[24] used different data sources in the patients' medical records and compared them with ICD codes retrieved from the hospital database and concluded that drug-related harms, although described in different documents, were well documented, however, less than 10% of the cases were reflected in the ICD codes in the electronic discharge summaries. Ackroyd-Stolarz et al[39] identified that their codes had 68% sensitivity and 90% specificity for detecting ADE. Osmont et al[30] identified that five codes (T88.6, L27.0, J70.4, G62.0, and N14.1) had a greater than 40% yield for identifying drug-induced liver injury, identifying about 79.5% of these events with these codes (criterion 6). Most of the selected articles (n=28, 84.8%) presented the limitations of the study (criterion 7).

Concordance Analysis

Chart 3 Characteristics of the articles included in the systematic review of ICD-10 codes as screening for Adverse Drug Events.

Study/ Country	Objective	ICDS selection method	No. of codes	Case Definition	Class	Sample Size	Measurement Frequency
Malpass et al. (1999) Austrália	Develop an ADE surveillance system.	Mixed	458	ADE is any event or circumstance, caused by health care	ADE	Not reported	Not reported
Cox et al. (2001) Inglaterra	Compare ADRs identified in DAH and DFV	Direto	175	Reaction to new drugs or severe reaction to any drug.	ADR	21,365 patients	0.2% of hospitalizations
CDC (2004) USA	Describe the rates of deaths from poisoning	Direto	152	Harmful effects due to pharmaceuticals, chemicals, illicit drugs.	INTOX	Not reported	5,0 - 7,8 / 100.000 deaths
Burgess *et al*. (2005) Austrália	Examine ADR hospitalization rates in persons ≥ 60 years of age	Direct	200-MA	WHO concept of ADR	ADR	População ≥ 60 anos	0.8% of the hospitalizations
Waller, *et al.* (2004) Inglaterra	Review hospitalizations as "drug-induced" and assess ADR burden.	Mixed	243	CID-10 com descrição "induzido por drogas" ou "devido a" medicamento e agrupamento "Y" da CID	ADR	53,847,408 records	0.4% of the hospitalizations
Lugardon *et al.* (2006) França	Estimate the incidence of severe ADRs	NR	299	WHO concept of ADR	ADR	261 patients	2,9% of the hospitalizations
Zhang, *et al.* (2006) Austrália	Assess ADR rates in rehospitalized elderly	Direct	175-MA	WHO concept of ADR	ADR	37,296 persons	18.4% of the hospitalizations
Patel *et al.* (2007) Inglaterra	Assess ADR hospitalization rate and accuracy of reports	Mixed	245	WHO concept of ADR	ADR	88,822,005 hospitalizations	0,5% of the hospitalizations
Rozenfeld, Suely. (2007). Brasil	Identify prevalence of in-hospital PRMs	Mixed	611	Hospitalizations with a PRM ICD diagnosis.	ADE	1,898,676 hospitalizations	0,18% of the hospitalizations
Lessa, M.A & Bochner, R. (2008) Brasil	Identify therapeutic classes that caused ADE in children <1 year	NR	430	Hospitalizations with ICD-10 diagnoses of ADE.	ADE	1,063 records	1,063 hospitalizations
Hodgkinson *et al.* (2009) Austrália	Compare the identification of ADR with ICD-10 and spontaneous reports	Direct	195	WHO concept of ADR	ADR	12,414 records	4.5% of the hospitalizations
Jones *et al.* (2013) USA	Describe the drugs involved in overdose deaths	Direct	319	Deaths with codes X40-X44, X60-X64, X85 and Y10-Y14, T36-T39, T40.2-T40.4, T41-T43.5 and T43.8-T50.8	INTOX	38,329 records of overdose deaths	57.7% of the deaths

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Hauck K, Zhao X (2011) Inglaterra	Relate the risk factors for ADRs, hospital infection and ulcers	Mixed	206-MA	Not reported	ADR	206,489 records	3.4% of ADRs/ 2 days of hospitalization
Mota et al. (2012) Brasil	Describe deaths from drug poisoning	Direct	327	deaths with ICD codes associated with drug intoxication.	INTOX	9,588,501 deaths	45.9 /100,000 Total deaths
Shepherd. et al. (2012) USA	Examine trends in mortality from ADRs	Direct	175	WHO concept of ADR	ADR	2.313.902.748 inhabitants/ year	0.12/100,000 Deaths
Hohl et al. (2013) Canadá	Determine the proportion of ADEs in emergency medical care.	Mixed	650-MG	Abnormal symptoms, signs or laboratory values due to the use of drugs	ADE	1,574 consultation records	14% emergency consultations
Nordstrom et al. (2013) USA	Describe the rates, causes, and circumstances of drug deaths.	Mixed	446	"Drug-induced deaths," and "drug-related deaths" from drug overdose	ADE	450,000 death records	4,828 deaths
Osmont, et al. (2013) França	Evaluate the performance of ICD-10 in PMSI for identifying severe ADR.	NR	234-MF	A drug that causes death, life-threatening, hospitalization, serious disability, or congenital anomalies.	ADR	383 patient records	Not reported
Ackroyd-Stolarz et al. (2014) Canadá	Validate ICD-10 codes for ADE, ulcer and falls in the hospital	Mixed	464	Injury caused by a drug	ADE	284 patient records	Sensitivity 0.68 and specificity 0.9
Durrieu et al. (2014) França	Detect ADRs in children at PMSI and compare with pharmacovigilance data	NR	129-MF	WHO concept of ADR	ADR	1,128 hospitalizations and 200 notifications	0,6% of the hospitalizations
Reynolds et al. (2014) Inglaterra	Examine record of drug harms in hospitalizations	NR	489	Medication harms are all ADRs, errors and poor adherence to treatment.	ADE	1,237 patients	5,2% of the hospitalizations
Parikh et al. (2014) Austrália	Use MACHADx2 to calculate incidence of hospital-acquired ADEs	Mixed	428	Injury from ADEs, medication administration errors or failures.	ADE	57,205 hospital discharges	0,7% of the hospitalizations
Stacey et al. (2014) Austrália	Compare ADEs in children with other reported events.	Direct	251	Injury from medical intervention related to a drug.	ADE	276 children	Not reported
Stausberg J. (2014) Alemanha	Compare the prevalence of ADE in hospitals in three countries.	Mixed	502 -MG	Injury from drug-related medical intervention.	ADE	29,557,748 registrations	5.3% of hospitalizations

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McKay et al. (2015) Inglaterra	Identify primary care factors with hospital admission for ADRs	Mixed	282	Codes of terms 'drug-induced or 'due to [drug]', 'adverse drug event' or code 'Y40-Y59'	ADR	53,422,119 patients	3.76 / 1,000 of hospitalizations
Amelung et al. (2017) Alemanha	Identify ICD-10 codes that describe preventable ADEs.	Mixed	363	Not reported or not clear.	ADE	54,032 patients	82.6 / 1,000 hospitalizations
Du W et al. (2017) Austrália	Evaluate the use of ICD-10 and diagnostic criteria in ADR hospitalizations.	Mixed	796	WHO concept of ADR	ADR	493,442 hospitalizations	10.4% of the hospitalizations
Hedegaard et al. (2018) USA	Describe drug overdose deaths.	Direct	176	Drug overdose deaths.	INTOX	Not reported	21.7 deaths /100,000 inhab.
Martins et al. (2018) Brasil	Examine the potential of using ICD-10 in hospital admission data.	Mixed	595	Drug/vaccine use that resulted in ADE.	ADE	55,604,537 hospitalizations	0.49% of the hospitalizations
Mota et al. (2018) Brasil	Propose an ICD code-list for the surveillance of ADE.	Mixed	691	ADR: WHO Concept Drug Poisoning - exposure to an amount of drug that can cause harm.	ADE	Not applicable	Not reported
Ock et al. (2018) Coreia do Sul	Identify ADEs, with ICD-10 Y-codes.	Direct	204	Adverse event occurring with ICD10 group Y code at diagnosis	ADE	20,817 registrations	0.18% of the registrations
Parameswaran et al. (2018) Austrália	Compare the identification of hospitalizations for ADR in the elderly with ICD-10.	Direct	195	WHO concept of ADR	ADR	768 patients	2.7% of the hospitalizations
Santos, G.A.S & Boing, AC. (2018) Brasil	Describe the trend of deaths and hospitalizations due to ADE in Brazil.	Direct	461	Unfavorable medical occurrence during a drug treatment.	ADE	11,018 deaths and 671,534 hospitalizations	0.1% of the deaths and 0.4% of the hospitalizations.

Legendas: RAM- Reação Adversa a Medicamentos, EAM- Eventos Adversos a Medicamentos, INTOX- Intoxicações e Envenenamentos, PRM- Problemas Relacionados a Medicamentos, MACHADx2-Classes de Agregação do Sistema de Classificação de Diagnósticos Adquiridos em Hospitais (CHADx) da Comissão Australiana de Segurança e Qualidade em Cuidados de Saúde (ACSQHC)

Three high density points (clusters) were observed in the frequency distribution of the ICD codes: the first with low (<25%) concordance values (n=681, 61.6%), which is equivalent, to grade 0 and 1, the second with median (50% to < 80%) concordance values (n=229, 20.7%) which is grade 2 and the third with high (>80%) concordance values (n=195, 17.7%), which is grade 3 (Figure 2).

When the frequency distribution for each individual class of ADE is evaluated, "ADR-external causes" stands out, with high concordance of all its ICD codes. The codes of the "intoxication" class with median concordance, while the code groups of "ADR-signs and symptoms", "personal history of drug allergy", and "medication error", in their majority, presented low concordance values. The classes "ADR-manifestation of illness," "other AE NCOP," and "medication abuse" were the classes that showed the greatest variability in concordance measures, but in general concentrating between low to median concordances. In view of this, it is worth noting that in all of these, the ICD codes are related to the class "allergy histories" and had insufficient concordance among the authors (Chart 5).

According to the classification adopted for the magnitude of concordance, it was observed that 681 (61.6%) codes were in the weak concordance grouping, 436 with insufficient concordance and 245 with low concordance; other 229 (20.8%) codes presented medium concordance and 195 (17.6%) codes were classified as high concordance (Chart 5).

DISCUSSION

This review study aimed to identify and analyze the concordance of ICD-10 codes that have been used as screeners for ADE. Among the 33 selected studies, 1,105 ICD-10 codes used for this purpose were identified. Only 38.4% of these codes presented with medium and high concordance among the studies. Overall, great variability was identified in the number and types of codes used, which may have contributed in large part to the variability of prevalence rates estimated for the events researched.

Whereas ADE is an important public health problem to be addressed[2,3,6], its underreporting represents a threat to collective and individual health. The adoption of new strategies for the early identification of these diseases, with the processing of large health databases, has been gaining efforts[50], in addition to the traditional resources involved in pharmacovigilance activities. Strategies of this nature need to be more widespread, especially in developing countries, because they are simple, fast and low-cost methods, and can contribute to the identification and prevention of ADEs[37].

The studies that used the direct method to track ADEs had a smaller average number of ICD codes selected compared to those that used the mixed method, and consequently obtained a lower prevalence in their outcome measures. This result was also identified in the study by Hohl et al, where the researchers concluded that variability in the definitions of the events of interest used, along with different methods for identifying the tracking codes, generate smaller or incomplete code sets, which reduces the ability to identify suspected cases and increases the heterogeneity of event prevalence results[8]. One of these reported problems could be identified during the quality assessment of the studies, since in part of the studies, the authors did not report sufficiently, or it was not clear how the codes were selected[8].

Following this, it was found that there is no consensus among health researchers about which ICD codes reliably identify adverse events, which leads to substantial variability in the procedures used for their identification and validation. This result was also demonstrated in the study conducted by Hohl et al[8]. Given this, in our review, only five (15.1%) studies estimated the sensitivity/specificity of their set of ICD codes. Therefore, the lack of validation of these codes hinders the understanding of the impact of their use in Pharmacovigilance, and points to the need to advance in this theme[51].

There are at least three ways to code ADEs using the ICD: identify the drug that caused an ADE using "external cause of injury codes"; identify the diagnosis of the disease caused by the drug using "disease manifestation codes" or associate these two codes: "external cause of injury codes" and "disease manifestation codes" indicating the patient's injury and diagnosis, respectively[8].

Ignorance of the multiple ways in which ADE can be coded may also compromise the validity and completeness of code selection or contribute to poor comparability between studies due to divergences in the estimates of different authors[8]. In this review it was possible to identify different methods of code selection used by the authors and with this diversity, both in the number of codes and in their specifications.

In the concordance analysis it was verified that 41.2% of the ICD codes were classified as "low concordance", even though they have in their description terms that clearly relate to the use of medication, such as "induced by drugs" or "due to drugs", as examples, the codes of the groupings X42, X44, X61 referring to accidental poisoning (intoxication) and I95.2 (hypotension due to drugs). Similarly, the codes for disease manifestations, known as severe AMS, such as polymorphous erythema (Lyell's syndrome (L51.2) and Stevens-Johnson syndrome (L51.1)) were frequently omitted in studies on ADR. Therefore, these results deserve better detailing in future studies.

One hypothesis that may explain the absence of codes related to intoxication is due to the fact that this event is not relevant from a traditional pharmacovigilance perspective, which focuses mainly on identifying ADRs and medication errors, leaving out other adverse events that are also related to the use of medicines[7], as well as the limitations inherent

Chart 4 Quality assessment of the primary studies included in the review.

Authors	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7
Malpass et al. (1999)	NC	Sim	NC	Sim	Não	Não	Não
Cox et al. (2001)	Sim	Não	Sim	Não	Sim	Não	Sim
CDC (2004)	NC	Sim	Sim	Sim	Sim	Não	Sim
Burgess et al. (2005)	Sim	Não	Sim	Sim	Sim	Não	Sim
Waller et al. (2005)	Sim	Não	Não	Não	Sim	Não	Sim
Lugardon et al. (2006)	Sim	Não	Sim	Sim	Não	Não	Sim
Zhang et al. (2007)	Sim	Não	Sim	Não	Sim	Não	Sim
Patel et al. (2007)	Sim	Não	Sim	Sim	Sim	Não	Sim
Rozenfeld, Suely (2007)	Sim	Sim	Sim	Sim	Não	Não	Sim
Lessa, M.A & Bochner, R. (2008)	Sim	Não	Sim	Sim	Sim	Não	Não
Hodgkinson et al. (2009)	Sim	Não	Sim	Sim	Sim	Não	Não
Jones et al. (2010)	Sim	Sim	Sim	Sim	Sim	Não	Sim
Hauck K, Zhao X (2011)	Sim	Não	Sim	Sim	Sim	Não	Sim
Mota et al. (2012)	Sim	Sim	Sim	Sim	Sim	Não	Sim
Shepherd et al. (2012)	Sim	Não	NC	Sim	Sim	Não	Sim
Hohl et al. (2013)	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Nordstrom et al. (2013)	Sim	Sim	Sim	Sim	Não	Não	Sim
Osmont et al. (2013)	Sim	Não	Sim	Não	Sim	Sim	Sim
Ackroyd-Stolarz et al. (2014)	Sim	Não	Sim	Sim	Não	Sim	Sim
Durrieu et al. (2014)	Sim	Não	Sim	Não	Sim	Não	Sim
Reynolds et al. (2014)	Sim	Não	Sim	Sim	Não	Sim	Sim
Parikh et al. (2014)	Sim	Sim	Sim	Sim	Sim	Não	Não
Stacey et al. (2014)	Sim	Não	Sim	Sim	Sim	Não	Sim
Stausberg J. (2014)	Sim	Sim	Sim	Sim	Não	Não	Sim
McKay et al. (2015)	Sim	Sim	NC	Sim	Não	Não	Sim
Amelung et al. (2017)	Sim	Sim	Sim	Sim	Não	Não	Sim
Du et al. (2017)	Sim	Sim	Sim	Sim	Sim	Não	Sim
Hedegaard et al. (2018)	NC	Sim	Sim	Sim	Sim	Não	Não
Martins et al. (2018)	Sim	Sim	Sim	Não	Não	Não	Sim
Mota et al. (2018).	NA	Sim	Sim	NA	Não	Não	Sim
Ock et al. (2018)	Sim	Não	Sim	Sim	Sim	Não	Sim
Parameswaran et al. (2018)	Sim	Não	Não	Não	Não	Sim	Sim
Santos, G.A.S & Boing, AC. (2018)	Sim	Não	Sim	Sim	Sim	Não	Sim

Legend: NA: Not Applicable (Not evaluated); NC- Unclear; Criteria used for quality assessment adapted from Cochrane bias guidelines from GRACE, Lorney Criteria, and York Center
1-Were the study design, sampling method or sample size appropriate to the research question?
2-Were the methods for identifying appropriate ICD-10 codes sufficiently detailed by the author and adequate to identify the health outcome?
3-Were preventive measures taken to minimize biases and errors in the study selection process?
4-Are the subjects and study setting described in detail and similar to those of interest to you and reflecting routine practice or the usual setting in which the intervention would be implemented?
5-Are the primary endpoints defined exclusively in the text description of the word “drug/drugs” in the ICD Code description?
6-Did the authors calculate the validity parameters (sensitivity and/or specificity) of the ICD codes selected or did they reference from other studies that validated the codes used?
7-Did the primary study report limitations?

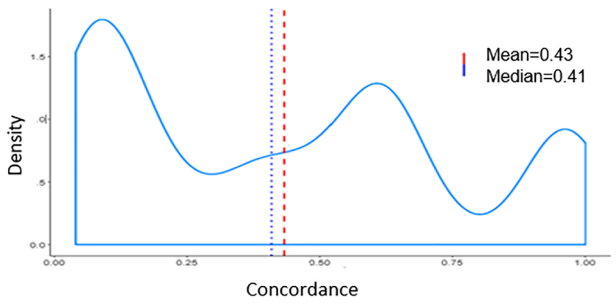

Figure 2 Analysis of the concordance in the total set of ICD-10 codes
Low concordance: concordance values below 25% among the researchers
Medium concordance: values between 50 to <80% concordance among the researchers
High concordance: values above 80% concordance among the researchers

in the operational definition of ADEs, which according to Hohls et al, this lack of consensus on the concept is one of the factors that can hinder the selection, thus suggesting a need for harmonization in the concept of ADE[8].

Finally, the codes with high concordance were all from the Y40-Y59 cluster, representing a great consensus among the authors, perhaps because the description of the cluster is the closest to the definition of ADR adopted by the WHO, which facilitates the recommendation to use these codes[52].

The purpose of this study was not to determine which ICD codes should be used in pharmacovigilance studies, but rather to systematize the knowledge and show the diversity of ICD codes that are used in the literature as tracers of ADEs, pointing out among them, which ones are more in concordance among the authors. However, future approaches will be necessary to seek consensus on these codes, to allow comparisons between different sites, and to analyze temporal trends that support decision making in pharmacovigilance.

The reflections present in this study may be important at this time of strengthening the culture of patient safety around the world, along with digital access to information, a consequence of the spread of electronic records and detailed and robust information systems related to patient health. This scenario expands the possibilities of using ICD codes as ADE trackers to complement existing spontaneous reporting systems, thus reducing ADE underreporting[33,51].

Although the method of tracing ADEs with ICD codes is feasible, fast and efficient, the use of this method is not without limitations and the results should be interpreted with caution, since diagnoses contained in hospital systems may be inaccurate[26,51], since these records are intended to meet administrative-financial demands and may distort information for other uses[45]. Caution should also be taken when using these codes suggested by international publications, since it is common for local adaptations to occur in ICD groupings, introducing additional variability in coding and making it difficult to interpret in other contexts[8].

In addition, there are the limitations of primary studies. The selection bias may have been derived from the search strategies and inclusion and exclusion criteria of the selected articles. Finally, the varied definitions of ADE used in the primary studies and the lack of detailed methods in the selection of codes in some primary studies may have allowed the inclusion of articles in which the authors only replicated the codes used by other authors, thus violating the principle of randomness required in the statistical analysis adopted (Bernoulli's tests). It is worth remembering that the transition from ICD-10 to ICD-11 is currently being carried out, a version that will be totally electronic and with significant improvements, which may overcome some limitations present in the use of ICD-10.

CONCLUSION

The synthesis of the ADE tracking codes identified here, with their respective levels of concordance, represents a simple and efficient method for capturing ADEs in large health databases, contributing to new researchers' ability to identify and form their groupings with codes that are more appropriate for their objectives, serving different purposes in health research and contributing to the reduction of underreporting of these events in traditional pharmacovigilance reporting systems.

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Chart 5 ICD-10 codes identified in the studies and classified according to the degree of concordance between the authors.

Nature of ADEs		Codes and their respective degree of concordance between the authors			
		0- Insufficient concordance	**1- Low concordance**	**2- Average concordance**	**3- High concordance**
ADR	ADR - Disease Manifestation (n=491)	Z03.6, D50.0, D61.9, D62, D65, D68.4, D68.8, D68.9, D69, D69.0, D69.2, D69.5, D69.6, D69.9, D74.8, E10.0-E10.9, E11.0-E11.9, E12.0-E12.9, E13.0-E13.9, E14.0-E14.9, E22.1, E28.0, E28.1, E29.1, E61, E86, E87, E87.0-E87.8,F12.2-F12.5,F12.7-F12.9, G21.2, G25.0, G25.3, G25.8, G40.5, G43,G43.0-G43.3, G43.9, G70.0, G92, G93.7, G95.8, H11.3, H18.0, H21.0, H31.3, H35.3, H35.6, H43.1, H53, H53.0, H53.1, H53.2, H53.3, H53.4, H53.5, H53.6, H53.8, H53.9, H92.2, I15.8, I15.9, I26.0, I26.9, I31.2, I44, I44.0-I44.7, I45, I45.8, I46.1, I47.2, I49, I49.0, I60, I61, I61.0-I61.9, I62, I80, I80.0-I80.3, I80.8, I80.9, I85.0, I95, I95.0, I95.1, I95.8, I95.9, J38.5, J45.0, J45.1, J45.8, J46, J80, J81, K03.2, K10.2, K22.1, K25, K25.0-K25.7, K25.9, K26, K26.0-K26.7, K26.9, K27, K27.0-K27.7, K27.9, K28, K28.0-K28.7, K28.9, K29.0,K52.1, K52.8, K52.9, K62.5, K66.1, K72.0, K72.9, K76.7, K85, K86, K92.0, K92.1, K92.2, L20, L20.0, L20.8, L20.9, L21, L21.0-L21.9, L26, L27, L28, L28.0-L28.2, L29, L29.0-L29.9, L30, L30.0-L30.9, L50.0, L51, L51.0, L51.8, L51.9, L52, L56.2, L65, L65.0, L68.0, L68.1, L71.0, L93, M25.0, M31.0, M62.8, M83.4, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.0, N18.8, N18.9, N19, N42.1, N62, N83.6, N83.7, N85.7, N89.7, N92.1-N92.4, N92.6, N93, N95.0, N95.3, N99.0, O26.6, O29.3, O68, O74.2, O74.3, O74.5, O74.6, O74.8, O74.9, O89, O89.0-O89.5, S06.4-S06.6, S06.8,Q73.1,F05, F05.0-F05.9,F16, F16.2-F16.9,F52,F52.0-F52.9, A80.0	A04.7, D52.1, D64.2, D68.3, D70, E03.2, E06.4, E15, E16.0, E23.1, E24.2, E66.1, F11, F11.2-F11.9, F13, F13.2-F13.9, F15, F15.2-F15.9, F19, F19.2-F19.9, G04.0, G44.4, G71.1, H26.3, H40.6, H91.0, I42.7, I95.2, K71, K71.1, K71.3-K71.6, K71.8, K71.9, K85.3, L10.5, L23.3, L24.4, L25.1, L27.8, L27.9, L43.2, L51.1, L51.2, L56.0, L64.0, M02.2, M34.2, M80.4, M81.4, M83.5, M87.1, N14, N14.0, N14.3, N14.4, O35.5, O74.4, P04.0, P04.1, P04.4, P58.4, P93, P96.1, P96.2, Q86.1, Q86.2	D59.0, D59.2, D61.1, E27.3, G21.0, G21.1, G24.0, G25.1, G25.4, G25.6, G62.0, G72.0-J70.4, K71.0, K71.2, K71.7, L27.0, L27.1, L56.1, M10.2, M32.0, N14.1, N14.2, T88.7	-
	ADR- Signs and Symptoms (n=53)	R00.1, R04.0, R04.1, R04.8, R04.9, R06.0, R06.8, R11, R17, R20, R20.0-R20.8, R21, R23, R23.0-R23.8, R31, R34, R40.0-R40.2, R41.0-R41.8, R42, R44, R44.0-R44.3, R44.8, R51, R55, R58, R73.9, R74.0, R78.1, R78.3, R78.4, R78.5, R78.6, R78.8, R82.5	-	-	-
	ADR-External Causes (n=195)	-	-	-	Y40-Y59.9
Sub- Total (n=722) / (% concordance)		**403 / (8,3%)**	**98 / (41,7%)**	**26 / (62,5)**	**195 / (96,2%)**
Abuse (n=7)		F12.1, F16.1	F11.1, F13.1, F15.1, F19.1, F55	**-**	**-**
Total codes / (%concordance)		**2 / (10,4%)**	**5 / (41,7%)**	**0 / (0,0%)**	**0 / (0,0%)**
Other AE NCOP (n=22)		T80, T80.0, T81.0, T81.1, T78, T78.8, T78.9, T78.2, T78.3, T78.4	T80.1, T80.2, T80.5, T80.6, T80.8, T80.9, T88.0-T88.2, T88.5	T88.3, T88.6	-

Continua...

...Continuação

Total codes / (%concordance)	**10 / (15,2%)**	**10 / (39,1%)**	**2 / (71,7%)**	**0 / (0,0%)**
Erro (n=11)	Y63.1, Y63.6, Y63.8, Y63.9, Y64.1, Y64.8, Y64.9, Y65.1	Y63.0, Y64.0, Y65.0	-	-
Sub Total / (% concordance)	**8 / (14,3%)**	**3 / (23,8%)**	**0 / (0,0%)**	**0 / (0,0%)**
Intoxications (n=332)	F12.0, F16.0	F11.0, F15.0, T40, T40.6, T40.7, T40.9, T96, X42, X42.0-X42.9, X44, X44.0-X44.9, X49.9, X61, X61.0-X61.9, X62, X62.0-X62.9, X64, X64.0-X64.9, X85, X85.0-X85.9, Y10, Y10.0-Y10.9, Y11, Y11.0-Y11.9, Y12, Y12.0-Y12.9, Y13, Y13.0-Y13.9, Y14, Y14.0-Y14.9	F13.0, F19.0, T36, T36.0-T36.9, T37, T37.0-T37.9, T38, T38.0-T38.9, T39,T39.0-T39.9, T40.2-T40.4, T41, T41.0-T41.5, T42, T42.0-T42.8, T43, T43.0-T43.9, T44, T44.0-T44.9, T45, T45.0-T45.9, T46, T46.0-T46.9, T47, T47.0-T47.9, T48, T48.0-T48.7, T49, T49.0-T49.9, T50, T50.0-T50.9, X40, X40.0-X40.9, X41, X41.0-X41.9, X43, X43.0-X43.9, X60, X60.0-X60.9, X63, X63.0-X63.9	-
Sub Total / (% concordance)	**2 / (12,5%)**	**129 / (40,9%)**	**201 / (64,0%)**	**0 / (0,0%)**
Personal history of drug allergies (n=11)	Z88-Z88.9	-	-	-
Sub Total / (% concordance)	**11 / (8,7%)**	**0 / (0,0%)**	**0 / (0,0%)**	**0 / (0,0%)**
Total codes (n=1,105)/ (% concordance)	**436 / (8,3%)**	**245 / (40,9%)**	**229 / (64,0%)**	**195 / (96,2%)**

* Median of Concordance for the grouping of the Codes

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ECD: Colaborou na concepção do estudo, análise dos dados e interpretação dos resultados, revisão e aprovação da versão final do manuscrito
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