Pharmacovigilance of drug-induced liver injury in search for frequency and outcomes in a Brazilian hospital: Challenges in future cases using a robust causality assessment method such as the updated RUCAM

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Abstract: *Background and Aims*: Drug-induced liver injury (DILI) is the main cause of drug withdrawal from the market. It is an adverse reaction that even when it was not observed in clinical trials, it can be subsequently detected when marketed. This study aimed to identify DILI frequency and outcomes evaluating various pharmacovigilance strategies.

Methods: A retrospective study was done evaluating strategies for screening DILI. The first strategy was based on gathering data from the ICDs related to toxic hepatitis K71 and acute liver failure K72 for 10 years. The second strategy was to gather 5 years of retrospective pharmacovigilance data. We excluded other hepatobiliary disorders as confounders.

Results: For K71 we identified 24 DILI cases from a total of 36, with one death. For K72, we found 15 DILI cases out of 300, with 8 deaths. Pharmacovigilance had 5,203 reports, 17 cases related to the hepatic system with nine DILI cases identified. DILI is estimated to occur around 21/100,000 patients but in reality, this frequency probably may be higher due to underreporting and underdiagnosing. There was no report of causality algorithm use.

Conclusions: The search through K71 was more sensitive, K72 detected the most severe cases, and the pharmacovigilance were the least severe. None DILI case identified by the ICD was reported in the pharmacovigilance and vice-versa, which gives evidence to the lack of interaction between the services and health professionals about adverse drug reactions. There was no record of the use of diagnostic algorithms to assess causality like the updated RUCAM (Roussel Uclaf Causality Assessment Method), a particular challenge for future DILI cases.

Keywords: Chemical and drug-induced liver injury, Pharmacovigilance, Pharmacoepidemiology, Pharmacy service hospital, Drug-related side effects and adverse reactions, Adverse drug reaction reporting systems, Roussel Uclaf Causality Assessment Method.

1. INTRODUCTION

Adverse drug reactions (ADRs) are considered a major problem due to their impact on the health system, as identified mainly in pharmacovigilance studies [1]. The frequency of ADRs as causes of hospital admissions varies from 2.3 to 21% [2-6]. In a meta-analysis, we found an incidence of 16.8% in the hospital setting [7]. Reported hospital mortality was between 4.3 and 10.2% [6-8,9]. Another meta-analysis reported the incidence of severe cases in 6.7% of hospitalized patients, this being considered one of the main causes of hospital mortality [10]. In the United States, for every dollar spent on drugs US$1.33 is spent to treat ADRs. It is estimated that drug-related problems in outpatients cost the health system more than US$177 billion [11]. The ADRs cost is estimated at around US$ 7.6 billion. There is an estimated cost reduction of around US$ 3.6 billion in the prevention of ADRs with the presence of a clinical pharmacist in the nursing units [12].

Among ADRs, drug-induced liver injury (DILI) is the main cause of failure in clinical research and drug withdrawal from the market [13,14]. In a review, of the 47 drugs withdrawn from the market, 32% were due to hepatotoxicity, while other studies that evaluated 462 medicinal products found hepatotoxicity as the major cause [15,16].

Studies in France and Iceland reported DILI incidences of 13.9/100,000 and 19.1/100,000 inhabitants/year [17,18]. In specific populations, such as people coinfected with the HIV virus and tuberculosis, the incidence may range from 7.8% to 22% [19,20]. Acute liver failure (ALF) is the most severe manifestation detected only after commercialization. Death and liver transplantation due

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E-ISSN: 2308-8044/20

to ALF occur at frequencies below 1 to 10,000 but are sufficient to compromise the safety of the drug [21].

This study aims to identify the frequency of drug-induced liver injury in a hospital as well as to compare different search strategies.

2. MATERIAL AND METHODS

We carried out a retrospective descriptive study following two different strategies for the detection of DILI in a Brazilian hospital group with 1,410 hospital beds.

The first strategy was to search for cases in a survey of the International Classification of Diseases (ICD). The search for patients by ICD was performed in the computerized system of the hospital. The first group consisted of patients diagnosed with ICDs related to toxic hepatitis K71.0 to K71.9 and the second group was related to acute liver failure comprising K72.0, K72.1, and K72.9. For both groups, the search occurred for a period of 10 years, from January 1, 2005, to December 31, 2015.

The second DILI identification strategy was based on pharmacovigilance data. The hospital group belongs to the network of sentinel hospitals and, since 2009, has a pharmacovigilance program to report adverse events directly in the hospital's computerized system. There is no restriction on the professional category, and the notification of adverse events is free. This strategy included cases of liver-related ADR reports. The data in the pharmacovigilance system consist of records of spontaneous notification and active search of hospital health professionals for a period of 5 years, from January 1, 2009 to December 31, 2014.

The exclusion criteria were patients with liver injuries defined by other etiologies such as alcoholic hepatitis, viral hepatitis, heart failure, pregnancy, autoimmune hepatitis, as well as cytomegalovirus, leptospirosis, Epstein Barr, hemolytic diseases, among other hepatobiliary disorders.

Data on the cases were extracted from the medical record and constituted patient profile data, symptoms, information regarding medication use, laboratory, image and biopsy exams, place of hospitalization, hospitalization time and outcome.

A descriptive statistical analysis of the data was carried out using the Excel 2013. For the sensitivity calculation we used data from 2011 to 2014, corresponding to the period in which it was possible to analyze all the strategies in the same period. This study was approved by the Ethics Committee by number 15230.

3. RESULTS

The search for ICD K71, in a 10-year period identified 36 patients; 24 (66.66%) of them had a suspicion of DILI in their medical record, according to

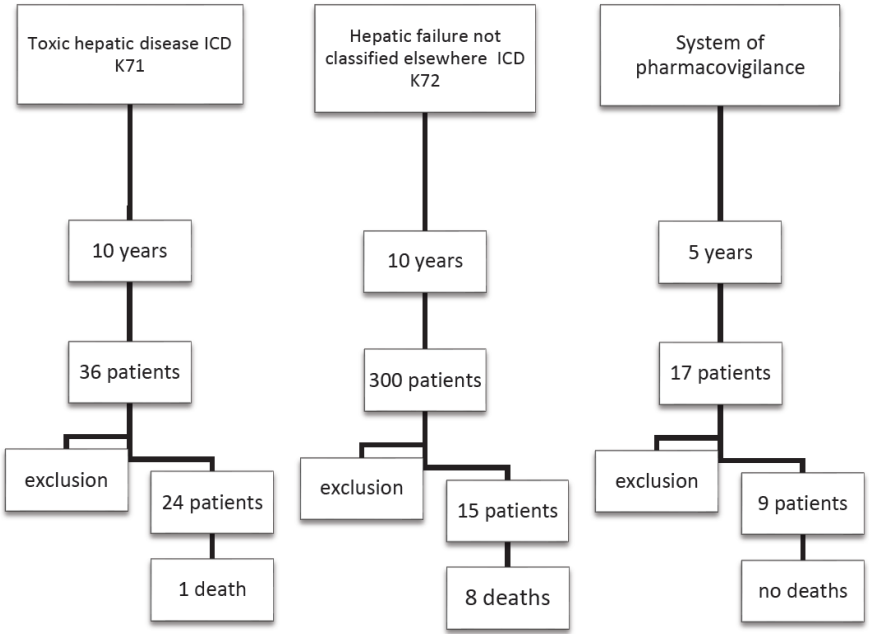

Figure 1: Flowchart of the drug induced liver injury cases identified through diagnosis of ICD K71, K 72 and the pharmacovigilance systems of a hospital group, in the period from 2005 to 2015.

Table 1: Characteristics of the Cases of Patients with Suspicion of Drug-Induced Liver Injury Detected by ICD K71 in the Period from 2005 to 2015 in the Hospital Group

Age/ Sex	Time in hospital (days)	Medication	Symptoms (days)	Clinical recovery (days)	Hepatic/ Extrahepatic onsets	outcome
72/ F	3	valproate	3	3	NI/jaundice, ABP, choluria	Δ
47/F	5	amitriptyline phenobarbital	NI	NI	ILT / ABP	Δ
44/F	15	AMOX /CLAV	9	NI	ILT / nausea, vomiting, diarrhoea, and ABP, jaundice	Δ
83/F	21	captopril	10	20	NI/ ABP, vomiting, and jaundice	Δ
67/F	15	CBP chlorpromazine	NI	NI	NI/ ABP, gastritis	Δ
33/M	6	CBP	3	5	ILT/skin rash, headache, fever	Δ
54/M	12	CBP, valproate amitriptyline	7	NI	ILT, AP, GGT and BT/ myalgia, anorexia, fever and chills jaundice, pruritus, choluria, and acholia	Δ
68/F	13	Guabiroba tea	5	13	NI/jaundice	Δ
52/F	20	chlorpromazine	10	3	ILT /hypotension, vomiting, and hiccup	Δ
30/M	14	chlorpromazine	7	10	NI/jaundice, nausea, vomiting, and pruritus	Δ
49/M	50	phenytoin	NI	18	Cholestasis, hepatomegaly, Increased LT, AP and BT/ EDO	Δ
60/F	13	fluoxetine	20	13	ILT / jaundice, acholuria, and ABP	Δ
10/M	1	isoniazid	2	1	ILT / anaemia, ABP, nausea vomiting fever	Δ
71/M	21	NI	14	NI	NI/ dyspnoea, ABP, and jaundice	Δ
70/F	5	norfloxacin	3	5	ILT, AP, BT/ haematuria and diffuse erythema vomiting jaundice	Δ
NB/M	1	TPN	NI	NI	NI/ NI	Δ
NB/F	19	TPN	NI	NI	NI/ NI	+
NB/F	8	TPN	NI	NI	Acholia jaundice/ NI	Δ
37/F	6	ACE	3	4	ILT/ nausea, vomiting, ABP	Δ
27/F	8	ACE	5	7	ILT and BT/ vomiting and nausea, jaundice and ABP	Δ
38/M	9	ACE; nimesulide, tylex®; AMOX	6	9	ILT/jaundice, nausea, vomiting, and ABP	Δ
46/F	10	ACDC; guarana; ACE	14	10	ILT/ acholuria, jaundice, nausea, vomiting epigastric pain	Δ
34/M	16	RIPE	NI	NI	ILT/ jaundice, vomiting, fever	Δ
30/F	17	thiamol	NI	7	ILT/AP and BT, jaundice, pruritus, and fever	Δ

+ : death; - Δ: hospital discharge; ABP: abdominal pain; ACDC: acetaminophen, carisoprodol, diclofenac, caffeine; ACE: acetaminophen; AMOX: amoxicilin AP: alkaline phosphatase; BT: total bilirubin; CBZ: carbamazepine; CLAV: clavulanate; EDO: Exfoliative dermatitis eosinophilia; F: female GGT: Gamma-Glutamyl transferase; ICD: International classification of diseases; ILT: increased liver transaminases; M: male; NI: not identified; TPN: total parenteral nutrition; RIPE: rifampicin, isoniazid, pyrazinamide and ethambutol; NB: new-born.

Figure **1**. Mortality was 1/24 (0.04%). The main drugs found were carbamazepine, chlorpromazine, paracetamol, and valproic acid (Table **1**).

For ICD K72, we found 300 patients and for 15 (5.00%) of these, there was suspicion of DILI. Mortality was 8/15 (53.00%) according to Figure **1**. Deaths occurred with the rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE), valproic acid, fluconazole, ketoconazole, sulfadiazine/Amoxycillin and clavulanate (Table **2**).

When the pharmacovigilance data were analyzed, we found that 5,203 notifications were performed in 5

Table 2: Characteristics of the Cases of Patients with Suspicion of Drug-Induced Liver Injury Detected by ICD K72 in the Period from 2005 to 2015 in the Hospital Group

Age/ Sex	Time in hospital (days)	Medication	Symptoms (days)	Clinical recovery (days)	Hepatic/ Extrahepatic onsets	outcome
29/M	28	valproate	NI	NI	increased AP/ jaundice, vomiting, nausea	+
28/F	2	valproate	NI	NI	ILT and BT/ acholia, epigastric pain and diarrhoea jaundice, choluria, fever, pruritus	Δ
10 Months/F	67	valproate	22	NI	ILT, BT and AP/ jaundice, fever	+
1/F	1	AMOX	10	NI	a nodular lesion in the liver/ vomiting, ABP	Δ
57/M	26	ketoconazole	NI	NI	Cirrhosis/ NI	Δ
50/F	13	diclofenac	NI	NI	ILT / constipation, dyspnoea, productive cough and dysphagia, nausea, vomiting, encephalopathy	Δ
5/M	30	fluconazole	NI	NI	increased GGT, GOT and Albumin/ jaundice, diarrhoea, pancytopenia	+
55/F	9	levofloxacin	NI	NI	NI/	Δ
50/F	2	nimesulide	360	NI	ILT and BT/ jaundice, ABP, asthenia, nausea and vomiting, encephalopathy	Δ
42/F	11	norfloxacin	15	NI	Hepatomegaly/ jaundice, fever, change in mental state	Δ
69/M	3	RIP	60	NI	NI/ jaundice	+
58/M	7	RIP	40	NI	ILT / jaundice, malaise, fever	+
53/M	40	RIP	15	NI	NI/ fever, anorexia, emaciation	Δ
38/M	44	RIP	NI	NI	NI/ abdominal distension, vomiting, and diarrhoea	+
26/M	16	sulfadiazine AMOX/CLAV	NI	NI	NI/ mild anaemia, oesophageal candidiasis	+

+: death; Δ: hospital discharge; ABP: abdominal pain; ACE: acetaminophen; AMOX: amoxicillin AP: alkaline phosphatase; BT: total bilirubin; CLAV: clavulanate F: female; GGT: Gamma-Glutamyl transferase; GOT: glutamic oxalacetic transaminase; HD: Hospital discharge; ICD: International classification of diseases; ILT: increased liver transaminases; M: male; NI: not identified; RIP: rifampicin, isoniazid, pyrazinamide; TPN: total parenteral nutrition.

years. Of the 17 cases related to the liver, 9 (52.94%) were associated with DILI, representing 0.17% of all reports. Other reports related to the liver have reported ascites, cirrhosis and liver decompensation by C virus and hyperbilirubinemia.

The pharmacist was the main notifier (n = 14), followed by the physician (n = 2), and the nurse (n = 1). All of the suspected patients progressed to cure, according to Figure **1**. The hepatotoxic drugs found were: Methotrexate, RIPE, rifampicin, isoniazid, pyrazinamide (RIP), acetaminophen, voriconazole, phenytoin, oxacillin together with azithromycin and chemotherapy with cyclophosphamide, vincristine, doxorubicin, cytarabine, and methotrexate. No report using a specific causality algorithm was identified.

We calculated the sensitivity for the identification of DILI for the three search strategies, being 50% with ICD K71, 31% with ICD K72, and 19% with pharmacovigilance data. The *kappa* agreement among the cases of hepatotoxicity identified by the ICD or by the notification system was 0. Therefore, no patient was diagnosed and notified at the same time.

Grouping the different strategies for identifying DILI we found 48 cases. The ICD most related to DILI was K71.0 toxic liver disease with cholestasis (n = 9). In 8/48 (16.6%) of the cases the patient died, of which, 7/8 (87.5%) had a diagnosis of acute liver failure K72. Anti-infective drugs were involved in 19/48 (40%) of the cases, followed by nervous system drugs 13/48 (27%) and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) and analgesics in 7/48 (15%). Regarding temporality and medication use, 20/48 (41%) of the patients did not identify the time of onset of symptoms since the use of the drug. In 29/48 (60%) of the patients, the time from the suspension of the drug and the clinical and/or laboratory improvement were not identified. We did not identify re-exposure to the suspected drug after suspension for suspected DILI.

Table 3: Characteristics of the Cases of Patients with Suspicion of Drug-Induced Liver Injury Detected from Pharmacovigilance in the Period from 2009 to 2014 in the Hospital Group

Age/Sex	Time in hospital (days)	Medication	Symptoms (days)	Clinical recovery (days)	Hepatic/ Extrahepatic onsets	outcome
60/F	30	phenytoin	NI	NI	ILT / fever, anaemia, constipation, hypoglycaemia	Δ
30/M	24	HyperCVAD	NI	NI	ILT / Febrile neutropenia	Δ
16/F	34	MTX	25	30	ILT / Febrile neutropenia, mucositis, musculoskeletal sternal pain	Δ
8/M	20	Oxacillin and azithromycin	11	NI	ILT / hepatic encephalopathy, increased submandibular volume, vomiting	Δ
51/F	4	ACE	NI	NI	ILT / Fever, night sweats, abdominal pain	Δ
36/F	40	RIP	NI	NI	ILT / TBC Neurological infection	Δ
25/M	37	RIPE	NI	7	ILT / pneumothorax, fever	Δ
75/F	13	RIPE	14	15	ILT / Severe anaemia pancytopenia	Δ
17/M	14	Voriconazole	14	NI	Increased AP/ Febrile neutropenia	Δ

+: death; Δ: hospital discharge; ABP: abdominal pain; ACE: acetaminophen; AP: alkaline phosphatase; F: female; HyperCVAD: cyclophosphamide, vincristine sulphate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; ILT: increased liver transaminases; M: male; MTX: methotrexate; NI: not identified; RIP: rifampicin, isoniazid, pyrazinamide; RIPE**:** rifampicin, isoniazid, pyrazinamide and ethambutol.

In 20/48 (41%) of the patients, the time of onset of symptoms from the use of the drug was not identified. In 29/48 (60%) of the patients, the time since the suspension of the drug and the clinical and/or laboratory improvement was not identified. The main form of identification of liver injury was the elevation of transaminases 31/48 (64.58%). Biopsies were performed in 5/48 (10.41%) of the patients. The most frequent extrahepatic manifestation was jaundice 28/48, (58.33%). Comorbidities found were mostly chronic or infectious diseases 26/48 (54.16%). Of the patients with DILI, 9/48 (18.75%) were positive for tuberculosis, 8/48 (16.66%) were positive for hepatitis C, and 6/48 (12.50%) of the patients were positive for HIV. We did not find exams for identifying tuberculosis, HIV, and hepatitis C, respectively in 35/48 (72.91%), 35/48 (72.91%) and 26/48 (54.16%) of the patients.

4. DISCUSSION

The prevalence of DILI was 39 cases in 10 years when analyzed only the ICDs but considering the pharmacovigilance data in a period of five years, we added nine more patients to this total. Since we evaluated the pharmacovigilance for a 5-year period, it would be possible to estimate a total of 57 cases of hepatotoxicity in a 10-year period, associating these two search strategies. In this situation, there would be an estimate of six patients per year. The estimated incidence of DILI in hospitalized patients would correspond to 0.02% of the hospitalizations per year or around 21/100,000 patients. A Chinese study found 92/100,000 patients [22]. Bjornsson, *et al*. found an incidence of 19.1/100,000 inhabitants in the general population. There seems to be a higher incidence of DILI in the hospital environment, probably due to the practice of polypharmacy, besides the fact that the hospital population has a larger portion of the chronically ill with health fragility than the general population. However, the Icelandic study found that 75% of the cases of DILI occurred with a single prescribed drug against 9% of polypharmacy [18].

A Swiss study with 4,209 patients found a DILI prevalence of 0.7% in hospital admission, while the incidence of hospitalized patients was 1.4% [23]. A Korean study found, retrospectively, 0.94% of DILI in 1,169 patients [24]. A Swiss study found a prevalence of 0.7% while the incidence of hospitalized patients was 1.4% in 4,209 patients, but this study found that about 60% of the cases of DILI are not recorded and were mentioned less than 9% in medical records. In the same study, the detection of DILI based on medical diagnoses and discharge records would have lost about 70% of cases [23]. In our study, in 10 years, we found 39 patients with K71 and K72 diagnoses. In a recent Chinese study, carried out in a hospital with around 1,200 beds, 287 patients with DILI diagnoses were found in 5 years [25]. In this Chinese study, the prevalence of diagnosis was 14.7 times higher than recorded, showing a great discrepancy in the records of DILI diagnoses. Sgro found a 16-fold difference in

incidence when compared to data from the sanitary authority [17]. The frequency found in this study was lower and can be explained by the possible high level of undiagnosed or non-notified cases.

Some patients with a suspicion of DILI do not present exams that may rule out other causes, and in many cases, they also evolve to death before taking the exams. In this situation, it is more difficult to detect DILI in the hospital emergency room, which is later detected during hospitalization depending on the clinician's ability and experience. The physician should determine the diagnosis according to the International Classification of Diseases (ICD), which includes DILI to code K71 – *toxic liver disease*, however, it may be diagnosed according to clinical manifestation on ICD K72 – *Hepatic failure not classified elsewhere*. When there is difficulty or uncertainty in the diagnosis, this could be recorded as K75.2 – *Non-specific reactive hepatitis*, among other ICDs when there is a certain degree of undefinition [26].

Another possibility is that DILI can be diagnosed as drug intoxication in ICDs T36 to T50 – *Intoxication by drugs, medication, and biological substances*. In addition to all these possible ICDs, DILI often does not correspond to the patient's main health problem, which is not registered in the secondary diagnoses [27,28]. Therefore, the difficulty of the diagnosis tends to be pulverized between different ICDs, hindering the search of the cases retrospectively.

In this study, there was a low sensitivity in the search for DILI cases when only one ICD was used as a search strategy or when the pharmacovigilance data were ignored. In a North American study evaluating different strategies for the detection of DILI by ICDs, low sensitivity was attributed when searched for ALF (Acute Liver Failure) only, but the combination of ICDs, including specific drug intoxication, can bring excellent results in the search for DILI. The efficiency of these methods is related to the correct diagnosis and the challenge is the lack of registration, which certainly makes a high sensitivity to DILI [26].

DILI had a lethality of 16.6%. In the literature, this lethality varies from 4 to 17% [28-30]. This high rate is attributed to the possible underreporting and underdiagnoses of the less severe cases and that evolved to a good outcome. Patients who developed DILI and progressed to ALF had a lethality of 53%. In a recent 5-year retrospective study, 35% who developed DILI developed ALF and progressed to transplantation or death [31]. Anti-infectives were related in 75% of the deaths by ALF. In the United States, paracetamol poisoning accounts for 42% of all cases, but we did not find paracetamol-related death in this study [32]. In another study, anti-infectives were responsible for 6% of the ALF cases by DILI [33], amoxicillin/clavulanate being the most frequent [29,34,35].

In this study, 5% of the patients with ALF were related to DILI. In a North American study of equal length, around 11% were related to DILI [28]. The difference in the data could be explained by the prospective design of the North American study, as the data do not suffer from information bias. Another point would be that the North American study was carried out in the specialized center.

Regarding the group of cases identified through pharmacovigilance, we found that 0.17% of ADR reports were DILI. In addition, an average of two reported cases of DILI per year. In the French pharmacovigilance database, cases of liver injury accounted for 13% of ADR reports for NSAIDs [36]. The pharmaceutical professional reported the most ADRs of liver injury. According to Barrit, *et al*., the pharmacist's assistance for DILI investigation in conjunction with the medical staff could reduce unnecessary examinations and invasive procedures that would result in increased costs and morbidity [37]. In agreement with Barrit, *et al*., this study suggests that the clinical pharmacist participates in the rounds and discussions of cases since often these are where the suspension or substitution of a drug with suspected hepatotoxicity are defined. The gathering of this information is of great importance to regulatory agencies since changes in the package insert, such as the inclusion of adverse reactions or change in frequency until withdrawal from the market depend on the information provided during the period of product marketing through pharmacovigilance.

Surprisingly, different databases can show different results. No patient diagnosed was notified, which can demonstrate the lack of communication between the different services and among the professionals. All the efforts in pharmacovigilance undertaken by the different Brazilian agencies between 2000 and 2010 still result in isolated results in some research groups, many health professionals are unaware of or do not identify the importance of the notification. This is, in part, perhaps due to the very disorganization of the flows in the services or by ignorance. On the other hand, medical records do not register notified cases. In

this sense, our study suggests that notified cases of ADRs be registered in the medical record, even if it was reported that the sanitary agency was notified about it.

The lacking use of algorithms likely does not represent a major demerit in relation to the diagnosis, because the lack of registration does not determine if there was use of algorithms. However, their use and record will provide a greater certainty to the diagnosis. The RUCAM (Roussel Uclaf Causality Assessment Method) algorithm has high sensitivity and specificity, being the most used causality assessment method in DILI cases. The prospective use of the updated RUCAM is strongly recommended, whereas applying it retrospectively is possible but should be avoided because this approach commonly provides low RUCAM based causality grading due to missing data [27].

There is great difficulty in retrospective studies due to poor information in records and lack of follow-up. Important information about the dosage of the suspected drug, other medications used by the patient, the temporal conditions involving the pharmacotherapy and the onset of symptoms are often not recorded [24,38]. In this study, there was a gap in relation to the recording of the time of onset of symptoms since the use of the drug and the time of suspension of the drug and the clinical and/or laboratory improvement. We suggest that these data can be identified and monitored by the clinical pharmacist and reported in medical records.

In addition, medication conciliation is a recommended clinical activity of the pharmacist, as it can be performed at hospital admission and can detect discrepancies in drug use, as well as ADRs. In a systematic review, the medication reconciliation showed a positive impact on the decrease in hospital visits related to adverse drug events, emergency care, and hospital readmission. In this sense, it is estimated that during the medication reconciliation it is a good alternative to obtain this data on the use of drugs and their temporal correlations in hospital admission, in addition to the investigation of potential confounding factors that may contribute to or are responsible for hepatotoxicity.

DILI cases occurred mainly in patients with chronic diseases, but it is noteworthy that almost half of the patients were not tested for hepatitis C, and most were not tested for HIV and tuberculosis. Considering that these populations comprise groups at risk for DILI [39], we strongly recommend virologic examinations, as requested in detail before [27].

Overall, this study presents the limitations typical to retrospective studies, related to the absence of data and information. In addition, we did not investigate *non-specific reactive hepatitis* K75.2 ICDs; T36 to T50 – *Intoxication by drugs, medication and biological substances*; as these are not considered a reference for DILI, but more underdiagnosed cases could be found; despite this, the data are consistent and resemble the literature.

5. CONCLUSION

The DILI prevalence found was low, but this result was probably attributed to the retrospective design, the lack of knowledge of the health professionals involved, and the difficulty in diagnosing and reporting cases of DILI. But it presented a little-known reality in Brazil, identifying some drugs associated with DILI such as valproic acid, carbamazepine, phenytoin, chlorpromazine, RIPE, amoxicillin and clavulanate, paracetamol, diclofenac, nimesulide, and captopril, among others.

The search for the ICD K71 was more sensitive to the identification of suspected DILI. ICD K72, despite detecting few cases, detected the most severe cases of patients who died. Regarding pharmacovigilance, less severe cases were reported, but the lack of overlap between the diagnosed and the notified patients confirms that these search methods are complementary and of great importance in the retrospective detection of DILI. None DILI case identifies by the ICD research strategy was reported in the pharmacovigilance database and vice-versa, which may demonstrate the lack of communication between the services and health professionals about adverse drug reactions. The cases identified no record of the use of algorithms to aid in the diagnosis of DILI, suggesting that this tool is still rarely used in clinical practice.

In this study, we estimated that the greater and more widespread the knowledge about DILI, the greater are the chances of early detection, adequate management and reduction of damages in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This study had no funding.

AUTHOR'S CONTRIBUTIONS

MWB and CRB participated in the conception, execution, and writing of the manuscript. LNF participated in data collection and approval of final manuscript writing

REFERENCES

[1] Hoffman KB, Dimbil M, Kyle RF, *et al*. A Drug Safety Rating System Based on Postmarketing Costs Associated with Adverse Events and Patient Outcomes. J Manag Care Spec Pharm 2015; 21: 1134-43c. https://doi.org/10.18553/jmcp.2015.21.12.1134

[2] Pirmohamed M, James S, Meakin S, *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329: 15-9. https://doi.org/10.1136/bmj.329.7456.15

[3] Hopf Y, Watson M, Williams D. Adverse-drug-reaction related admissions to a hospital in Scotland. Pharm World Sci 2008; 30: 854-62. https://doi.org/10.1007/s11096-008-9240-5

[4] van der Hooft CS, Dieleman JP, Siemes C, *et al*. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 2008; 17: 365-71. https://doi.org/10.1002/pds.1565

[5] Alexopoulou A, Dourakis SP, Mantzoukis D, *et al*. Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. Eur J Intern Med 2008; 19: 505-10. https://doi.org/10.1016/j.ejim.2007.06.030

[6] Pedrós C, Formiga F, Corbella X, Arnau JM. Adverse drug reactions leading to urgent hospital admission in an elderly population: prevalence and main features. Eur J Clin Pharmacol 2016; 72: 219-26. https://doi.org/10.1007/s00228-015-1974-0

[7] Miguel A, Azevedo LF, Araujo M, Pereira AC. Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2012; 21: 1139-54. https://doi.org/10.1002/pds.3309

[8] Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R. Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). BMC Health Serv Res 2010; 10: 287. https://doi.org/10.1186/1472-6963-10-287

[9] Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother 2008; 42: 1017-25. https://doi.org/10.1345/aph.1L037

[10] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279: 1200-5. https://doi.org/10.1001/jama.279.15.1200

[11] Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc 2001; 41:192-9. https://doi.org/10.1016/s1086-5802(16)31229-3

[12] Bootman JL, Harrison DL, Cox E. The health care cost of drug-related morbidity and mortality in nursing facilities. Arch Intern Med 1997; 157: 2089-96.

[13] Goldkind L, Laine L. A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: lessons learned from the bromfenac experience. Pharmacoepidemiol Drug Saf 2006; 15: 213-20. https://doi.org/10.1002/pds.1207

[14] Stevens JL, Baker TK. The future of drug safety testing: expanding the view and narrowing the focus. Drug Discov Today 2009; 14: 162-7. https://doi.org/10.1016/j.drudis.2008.11.009

[15] Olivier P, Montastruc JL. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. Pharmacoepidemiol Drug Saf 2006; 15: 808-12. https://doi.org/10.1002/pds.1248

[16] Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med 2016; 14: 10. https://doi.org/10.1186/s12916-019-1294-9

[17] Sgro C, Clinard F, Ouazir K, *et al*. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002; 36: 451-5. https://doi.org/10.1053/jhep.2002.34857

[18] Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25, 25. e1-3; quiz e19-20. https://doi.org/10.1053/j.gastro.2013.02.006

[19] Mugusi S, Ngaimisi E, Janabi M, *et al*. Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. PloS one 2012; 7: e40180. https://doi.org/10.1371/journal.pone.0040180

[20] Yimer G, Gry M, Amogne W, *et al*. Evaluation of patterns of liver toxicity in patients on antiretroviral and anti-tuberculosis drugs: a prospective four arm observational study in ethiopian patients. PloS One 2014; 9: e94271. https://doi.org/10.1371/journal.pone.0094271

[21] Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using controlled clinical trials to learn more about acute drug-induced liver injury. Hepatology 2008; 48: 1680-9. https://doi.org/10.1002/hep.22633

[22] Ou P, Chen Y, Li B, *et al*. Causes, clinical features and outcomes of drug-induced liver injury in hospitalized patients in a Chinese tertiary care hospital. Springer Plus 2015; 4: 802. https://doi.org/10.1186/s40064-015-1600-8

[23] Meier Y, Cavallaro M, Roos M, *et al*. Incidence of drug-induced liver injury in medical inpatients. Eur J Clin Pharmacol 2005; 61: 135-43. https://doi.org/10.1007/s00228-004-0888-z

[24] Woo HJ, Kim HY, Choi ES, *et al*. Drug-induced liver injury: A 2-year retrospective study of 1169 hospitalized patients in a single medical center. Phytomedicine 2015; 22: 1201-5. https://doi.org/10.1016/j.phymed.2015.10.002

[25] Chen SS, Yu KK, Huang C, *et al*. The characteristics and clinical outcome of drug-induced liver injury in a Chinese hospital: A retrospective cohort study. Medicine 2016; 95: e4683. https://doi.org/10.1097/md.0000000000004683

[26] Jinjuvadia K, Kwan W, Fontana RJ. Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury. Am J Gastroenterol 2007; 102: 2437-43. https://doi.org/10.1111/j.1572-0241.2007.01456.x

[27] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: The update. Int J Mol Sci 2016; 17(1): 14. https://doi.org/10.3390/ijms17010014

[28] Andrade RJ, Lucena MI, Fernandez MC, *et al*. Drug-induced liver injury: an analysis of 461 incidences submitted to the

Spanish registry over a 10-year period. Gastroenterology 2005; 129: 512-21. https://doi.org/10.1053/j.gastro.2005.05.006

[29] Bessone F, Hernandez N, Lucena MI, Andrade RJ. The Latin American DILI Registry Experience: A Successful Ongoing Collaborative Strategic Initiative. Int J Mol Sci 2016; 17: 313. https://doi.org/10.3390/ijms17030313

[30] Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. https://doi.org/10.1038/ajg.2010.287

[31] Baekdal M, Ytting H, Skalshøi Kjær M. Drug-induced liver injury: a cohort study on patients referred to the Danish transplant center over a five-year period. Scand J Gastroenterol 2017; 52: 450-4. https://doi.org/10.1080/00365521.2016.1267790

[32] Larson AM, Polson J, Fontana RJ, *et al*. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005; 42: 1364-72. https://doi.org/10.1002/hep.20948

[33] Goldberg DS, Forde KA, Carbonari DM, *et al*. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. Gastroenterology 2015; 148: 1353-61. e3. https://doi.org/10.1053/j.gastro.2015.02.050

[34] Bjornsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci 2016; 17: 224. https://doi.org/10.3390/ijms17020224

[35] Chalasani N, Bonkovsky HL, Fontana R, *et al*. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. e7. https://doi.org/10.1053/j.gastro.2015.03.006

[36] Bareille MP, Montastruc JL, Lapeyre-Mestre M. [Liver damage and nonsteroidal anti-inflammatory drugs: case non-case study in the French Pharmacovigilance Database]. Therapie 2001; 56: 51-5. https://doi.org/10.1053/j.gastro.2015.03.006

[37] Barritt AS, Lee J, Hayashi PH. Detective Work in Drug-induced Liver Injury: Sometimes It's All about Interviewing the Right Witness. Clin Gastroenterol Hepatol 2010; 8: 635-7. https://doi.org/10.1016/j.cgh.2010.03.020

[38] Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. https://doi.org/10.1002/hep.23937

[39] Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000; 283: 74-80. https://doi.org/10.1001/jama.283.1.74

Received on 11-09-2020 Accepted on 24-09-2020 Published on 08-10-2020

DOI: https://doi.org/10.12970/2308-8044.2020.08.08