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The relationship between potential drug-drug interactions and mortality rate of elderly hospitalized patients

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ABSTRACT

Background. The increase in drug-drug interactions (potential DDIs) is a consequence that older adults experience by high availability of prescription medications for an increasing variety of diseases. This increase in potential DDIs could be associated with mortality rate during hospitalization. **Objective**. To determine whether the association between the presence of Potential DDIs and mortality rate in hospitalized elderly and to describe the frequency of potential DDIs and characterize drugs. **Material and methods**. A retrospective research was performed by reviewing the medical records of patients 60 years and older who were admitted to a second-level care hospital. The Potential DDIs were identified through the Micromedex® program. Comorbidity was classified according to the Charlson Index (CCI). Other variables such as gender, age, number and type of drug, type of interaction, and duration of hospital stay were evaluated. **Results.** 505 patients were included, among whom the 62.77% presented at least one type of DDI. We found that 15.25% of moderate interactions were due to the combined use of angiotensin converting enzyme inhibitors and loop diuretics. Among serious interactions, 14.92% occurred due to the combined use of fluroquinolones and hypoglycemic agents. The duration of stay and a high comorbidity score, the presence of three or more interactions and exposure time to the interaction, were independently associated with mortality rate. **Conclusions**. This work shows that the occurrence of potential DDIs in the hospital environment for the elderly population is frequent and may be implicated in the cause of death for these patients.

Key words. Older adults. Comorbidity. Quality of medication. Potentially inappropriate drugs. Adverse reactions.

Las interacciones potenciales fármaco-fármaco están asociadas a la mortalidad hospitalaria en adultos mayores hospitalizados

RESUMEN

Antecedentes. El aumento de las interacciones potenciales fármaco-fármaco (potenciales DDI) es una consecuencia que los adultos mayores experimentan por un mayor número de medicamentos prescritos para una creciente variedad de enfermedades. Este incremento podría estar asociado con muerte hospitalaria. Objetivo. Determinar si existe asociación entre la presencia de potenciales DDI y muerte hospitalaria en adultos mayores, así como describir la frecuencia de las potenciales DDI y caracterizar a los fármacos prescritos. Material y métodos. Estudio retrospectivo mediante la revisión de expedientes de pacientes de 60 años o más que fueron ingresados en un hospital de segundo nivel. Las potenciales DDI fueron identificadas a través del programa Micromedex®. La comorbilidad se clasificó con el Índice de Charlson (ICC). Otras variables como el sexo, edad, número, tipo de fármaco, tipo de interacción y duración de la estancia hospitalaria fueron evaluados. Resultados. 505 pacientes fueron incluidos, entre los cuales 62.77% presentaron al menos un tipo de potenciales DDI. El 15.25% de las interacciones moderadas se deben a la utilización combinada de inhibidores de la enzima convertidora de angiotensina con diuréticos de asa. Entre las interacciones graves, 14.92% se debió a la utilización combinada de fluroquinolonas con hipoglucemiantes. La duración de la estancia, alta comorbilidad, presencia de tres o más interacciones y mayor tiempo de exposición a la interacción, se asociaron, independientemente, con muerte hospitalaria. Conclusiones. La presencia de potenciales DDI en adultos mayores es frecuente y puede estar implicada en la causa de muerte en estos pacientes.

Palabras clave. Adultos mayores. Comorbilidad. Calidad de la prescripción. Fármacos potencialmente inadecuados. Reacciones adversas.

INTRODUCTION

Although drugs have contributed to better disease management, they often have undesirable, harmful effects such as adverse drug events (ADEs). These may occur as adverse reactions (unpreventable) or as medication errors (MEs) (preventable) such as those causing drug-drug interactions (DDIs).[1]

Potential DDIs defined as the presence of a minimum 5-day overlap in days supply for drugs in an interacting pair[2] among the elderly population are increasingly common and are an important issue to address; the increase in potential DDIs is a consequence of an aging population that experiences physiological deterioration (i.e. reduction in renal and hepatic clearance) and the availability of prescription medications for an increasing variety of diseases. This combination of factors results in a polypharmacy, poor quality prescription drugs in the elderly population and the possibility of potential DDIs and drug problems, among other issues.[3-4]

In the hospital environment, between 3 and 73% of the elderly have experienced potential DDIs. This variation depends on the characteristics of the patient, the nature of the reaction, the method utilized for the classification of the interactions, the characteristics of the prescribing personnel, and the hospital itself.[5-9] In the community, these types of events are responsible for 5% of hospital admissions;[10] however, the association of potential DDIs with patient mortality has not been carefully evaluated because this requires rigorous surveillance of a large number of patients and careful monitoring of the apparent effects of each medication administered.

Three studies have found a lack of an association between inappropriate prescriptions or drug interactions and mortality rate.[11-13] However, these findings are limited by the study design as well as the criteria utilized for characterizing the drugs and their effects on patients.

OBJECTIVE

The objective of this work was to determine whether the association between the presence of potential DDIs and mortality rate in the hospital environment and to characterize the implicated drugs of the patients.

MATERIAL AND METHODS

Participants

A retrospective research was performed by reviewing the all medical records of patients 60 years and older who were admitted between January 1 and December 31 2004 (n = 7,540) in the Mexican Institute of Social Security (IMSS). For this study we obtained a list containing the file number, name and age of all patients admitted in 2004 and were randomly selected records entering the study.

The IMSS was created by law in 1943, composed by the government, employers, and employees like a social security system. Workers, their parents, and other close relatives are assigned to a Family Medicine Unit, which is the primary health care provider. Mexico City has a population of nearly 860,000 adults aged 60 years and older; 418,000 (48.6%) are affiliated to the IMSS. IMSS has 16 general hospitals in Mexico City. From those, the General Hospital Dr. Carlos MacGregor Sánchez Navarro was selected. This hospital is one of the biggest hospitals in Mexico City and it has 278 total beds. A total of 465 physicians and 705 nurses work there. Specialties as internal medicine, surgery, intensive care, pediatrics, among some others subspecialized services integrate the services provided.

We estimate the power of the sample with 105 cases assuming the following data the probability of exposure among controls is 0.4. The true odds ratio for disease in exposed subjects relative to unexposed subjects 2, obtained a power of 88%.[14]. These files were randomly selected by table of random numbers.

Inclusion criteria

Patients aged 60 and older, that were admitted to the Internal Medicine Service. Medical records of patients with incomplete medical records and information of medication illegible were excluded.

Each medical record included the following information:

- Duration of hospital staying.
- The characteristics of the patient: gender, age, diagnosis at admission/discharge [according to the International Classification of Diseases, Tenth Revision (ICD-10)].[15]
- Characteristics of the drug: number and type of drugs prescribed daily during total hospital stay, route of administration, dosage and admission and discharge diagnosis.

Based on information from paper medical records were collected every day each of the prescriptions by general practitioners trained for this. Once the data were obtained, based on this information the interactions were assessed by geriatricians.

Data collection

- ***Mortality.*** Mortality during hospitalization was defined as the death of a patient 48 hrs after admission.
- ***Drug classification.*** Drugs prescribed during the patient's entire hospital stay were classified using the Anatomical Therapeutic Chemical (ATC) Classification System.[16] This is a system instituted by the World Health Organization and includes an index of pharmacological substances and drugs organized by therapeutic groups. The drugs are divided into five different groups based on organ or the physiologic system on which they act and/or their therapeutic and chemical characteristics. The ATC code of each patient was identified based on the type and amount of the administered drug; the code considers the 14 groups or codes of the first level of ATC classification which makes reference to the organ or system in which the medicine acts.
- ***Potential Drug-Drug Interactions.*** A group of three nurses with degrees were previously trained and standardized to obtain information from records about potential drug-drug interactions. Nurses were reviewed by two geriatricians the inter-rater agreement was determined by Kappa coefficient for both groups; the result was 85 and 93%, respectively. They identified and classified in the potential drug-drug interactions using the electronic database Thomson Micromedex®.[17] It is an information platform generated through impartial analysis of clinical evidence and displays drug relationships so that clinics can test for interactions among different drugs, their effects, and their clinical significance. Drug-drug interactions were calculated by DROGAS-REAX® System,[17] which provides drug-drug, drug-foods, drug-illnesses, drug-alcohol, and drug-laboratory test drug interactions. For the purposes of this work, interactions were classified according to their severity, based in the criteria established by the aforementioned platform, where these were:

  - *Serious.* When the interaction threatened the life of the patient and/or required medical attention and/or a change in therapy.
  - *Moderate.* When the patient's condition worsened and/or when a change in therapy was required.
  - *Mild.* When the clinical effects were limited and included an increase in the frequency or severity of side effects yet did not require changes in therapy.

- ***Exposure time to potential DDIs.*** The exposure time was defined as number of days each patient received the drug combination that caused some interaction during his hospital staying, the interaction was identified and classified by geriatricians from the date of hospital discharge until first day of admission.
- ***Comorbidity.*** Comorbidity was evaluated by the Charlson Index and included nineteen diseases; the conditions of the patient were adapted to the codes of the ICD-10, and this adaptation was based on the list of clinical conditions and their descriptions[18] translated from the Charlson Index based on the ICD-9 version.[19] A score of 1, 2, 3 or 4 was assigned to each condition based on severity. The gravity of comorbidity was defined as: 1 = not severe, 2 = light, 3 = moderate, 4 = severe. The variable was dichotomized for analysis as low comorbidity ($\leq$ 2 points) and high comorbidity ($\geq$ 3 points).[19]

Statistical analysis

Descriptive analyses were performed using the patients' demographic and clinical data as well as the characteristics of the medications utilizing percentages and averages ($\pm$ SD) and corresponding confidence intervals of 95% or some other range. Normal distribution of this discrete variables was verified by Kolmogorov-Smirnov. To estimate the effect of the covariates on the occurrence of potential DDIs, univariate analyses were performed using logistic regression models.

In the multivariate logistic regression model, the potential confounders were those related to potential DDIs with $p < 0.05$ in the univariate analyses. The discrete variables were dichotomized using their average value as the cut point. The logistic regression model for discharge due to death began with all variables, which were consecutively eliminated according to statistical significance.

The final model was evaluated by the coefficient of probability test. The odds ratio and 95% confidence intervals (95% CI) were obtained from the β coefficients and their standard errors, respectively. Statistical analyses were performed using SPSS version 13 for Windows.[20]

This project was approved by and registered with the research and ethics committee of the 3rd and 4th delegation of the IMSS 2005-3607-0020.

RESULTS

In this work, 532 medical records of all elderly patients hospitalized in the Internal Medicine Department between January 1 and December 31 2004 were reviewed; 27 (5.0%) were eliminated because the medication information was imprecise or illegible, leaving a total of 505 patients 60 years and older, 277 (54.9%) of whom were female. The average age of the patients was 76.0 ± 8.8 SD, and the most frequent reason for admission was stroke at a frequency of 11.29% (57/505), followed by chronic obstructive pulmonary disease at 8.71% (44/505) and heart failure at 8.12% (41/505). The average hospital stay was 7.6 ± 3.4 SD days, and patients were administered an average of 6 ± 2.51 SD medications. Concerning prescriptions, 6,267 were analyzed, and these involved 212 active ingredients; overall, there were 15,456 administrated doses and 3,534 (56.39%) registered potential interactions. Of potential DDIs, 2,609 (41.63%) were classified as moderate and 925 (14.75%) severe during the hospital stay. Mild interactions were not found.

Of the 505 patients included in the work, 317 (62.77%) presented at least one type of interaction. Specifically, 122 (38.5%) patients presented a single moderate interation, 138 (43.5%) presented only one severe interaction and 57 (17.9%) presented both interactions (moderate and severe).

Of the moderate interactions, 15.29% occurred after the combined use of angiotensin converting enzyme (ACE) inhibitors and loop diuretics. With respect to the severe interactions, 14.92% occurred after the combined use of fluoroquinolones and hypoglycemic substances. These are shown in tables 1 and 2. Of all the medical records reviewed, 400 (79.20%) patients were discharged for causes other than death, and 105 (20.79%) were discharged due to death. Of the total deaths (n = 105), 54 were female and 51 male. In this group the average age was 75.3 ± 9.3, and there were no significant differences between the two groups based on age or gender. In this group the average number of administered medications was 14.0 ± 4.9 SD, and the average hospital stay was 6.3 ± 3.0 SD days.

The most common reason for admission was stroke at 8.8% (10/105), followed by pneumonia at 8% (5/105), acute myocardial infarction at 6% (6/105), and decompensated diabetes at 7% (7/105). The medications most frequently administered according to the first ATC classification group were for the cardiovascular system

Table 1. Moderate interactions and their clinical effects.*

Interaction types	Clinical effect	Interaction, n (%)	Patient, n (%)
• Angiotensin converting enzyme inhibitors and loop diuretics.	• Increased risk of hypotension.	399 (15.29)	27 (22.07)
• Low molecular weight heparins and salicylates.	• Increased risk of bleeding and increased risk of hematoma when neuraxial anesthesia is employed.	312 (11.96)	28 (23.00)
• Captopril and aspirin.	• Decreased captopril effectiveness.	235 (9.01)	18 (14.78)
• Aspirin and enalapril.	• Decreased enalapril effectiveness.	158 (6.06)	12 (9.53)
• Furosemide and digoxin.	• Digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	139 (5.33)	6 (5.16)
• Furosemide and aspirin.	• Blunting of diuretic effect of furosemide.	111 (4.25)	8 (6.91)
• Antidiabetic agents and beta-adrenergic blockers.	• Hypoglycemia, hyperglycemia, or hypertension.	66 (2.53)	2 (1.95)
• Aspirin and insulin.	• Hypoglycemia (CNS depression, seizures).	56 (2.15)	1 (1.08)
• Nonsteroidal anti-inflammatory agents and loop diuretics.	• Decreased diuretic and antihypertensive efficacy.	54 (2.07)	2 (1.66)
• Digoxin and metoclopramide.	• Decreased digoxin levels.	41 (1.57)	5 (4.08)
• Aspirin and diclofenac.	• Reduced diclofenac efficacy.	33 (1.26)	4 (3.21)
• Dihydropyridine calcium channel.	• Hypotension and/or bradycardia.	33 (1.26)	4 (3.21)
• Blockers and beta-adrenergic blockers amikacin and furosemide.	• Ototoxicity and/or nephrotoxicity.	33 (1.26)	2 (2.04)
• Levodopa and metoclopramide.	• Increased levodopa bioavailability and increased incidence of extrapyramidal symptoms.	28 (1.07)	2 (1.46)
Total		2,609	122 (38.5)

*According to the classification adopted by Moore LL, Minne K, Moore KB. DRUG-REAX System. Greenwood Village, CO: Micromedex; 2001.

Table 2. Severe interactions and their clinical effects.*

Interaction types	Clinical effect	Interaction, n (%)	Patient, n (%)
• Fluoroquinolones and antidiabetic agents.	• Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.	138 (14.92)	24 (17.7)
• Low molecular weight heparins and anticoagulants.	• Increased risk of bleeding.	136 (14.70)	26 (18.6)
• Low molecular weight heparins and nonsteroidal anti inflammatory agents.	• Increased risk of bleeding.	82 (8.86)	16 (11.8)
• Potassium-sparing diuretics and angiotensin converting enzyme inhibitors.	• Hyperkalemia.	78 (8.43)	13 (9.6)
• Beta-adrenergic blockers and beta-2 agonists.	• Decreased effectiveness of either the beta-adrenergic blocker or the beta-2 agonist.	49 (5.30)	9 (6.8)
• Digoxin and spironolactone.	• Digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	43 (4.65)	9 (6.8)
• Digoxin and erythromycin.	• Increased digoxin levels and digoxin toxicity (nausea, vomiting, arrhythmias).	41 (4.43)	5 (3.6)
• Potassium and captopril.	• Hyperkalemia.	37 (4.00)	7 (5.0)
• Opioid analgesics and benzodiazepines.	• Additive respiratory depression.	24 (2.59)	11 (7.7)
• Cinarizine and haloperidol.	• Increased sedative effects of cinarizine.	16 (1.73)	4 (2.7)
• Erythromycin and antipsychotics.	• Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).	15 (1.62)	3 (2.3)
• Enalapril and potassium.	• Hyperkalemia.	13 (1.41)	5 (3.6)
• Opioid analgesics and opioid agonists/antagonists.	• Precipitation of withdrawal symptoms (abdominal cramps, nausea, vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection).	12 (1.30)	3 (2.3)
• Tricyclic antidepressants and antipsychotics.	• Increased risk of cardiotoxicity (QT prolongation, torsades of pointes, cardiac arrest).	12 (1.30)	1 (0.5)
• Fluconazole and antipsychotics.	• Increased risk of cardiotoxicity (QT prolongation, torsades of pointes, cardiac arrest).	11 (1.19)	2 (0.9)
Total		925	138 (43.5)

*According to the classification adopted by Moore LL, Minne K, Moore KB. DRUG-REAX System. Greenwood Village, CO: Micromedex; 2001.

Table 3. Analysis crude for explorer the relationship between potential DDIs and discharge death.

Variables	Reason for discharge			
	Other cause 400, n (%)	Death 105, n (%)	OR (CI 95%)	p
• Patient characteristics				
Gender				
Female	223 (55.8)	54 (51.4)		
Male	177 (44.2)	51 (48.6)	1.19 (0.77-1.83)	0.496
Age				
≤ 75 years	208 (52.0)	11 (46.5)		
≥ 76 years	192 (48.0)	94 (89.5)	9.25 (4.81-17.81)	< 0.001
Days of hospitalization				
≤ 5 days	129 (32.2)	12 (10.5)		
≥ 6 days	271 (67.8)	93 (89.5)	4.06 (2.10-7.86)	< 0.001
• Characteristics of the prescription				
Number of medications				
≤ 7	96 (24.0)	14 (13.3)		
≥ 8	304 (76.0)	91 (86.7)	2.05 (1.11-3.76)	< 0.001
Number of codes of the first level of ATC				
≤ 5	194 (48.5)	12 (11.4)		
≥ 6	206 (51.5)	93 (31.1)	7.29 (3.87-13.73)	< 0.001
• Characteristics of the medicine				
Medicine of the digestive and metabolism system group (group A of the ATC)	165 (41.8)	85 (81.00)	6.05 (3.57-10.24)	< 0.001
Medicine of the cardiovascular system group (group C of the ATC)	106 (26.5)	49 (46.7)	2.42 (1.55-3.78)	< 0.001
Medicine of the nervous system group (group N of ATC)	44 (11.0)	33 (31.4)	3.70 (2.21-6.22)	< 0.001
• Most frequent medications				
Furosemide	220 (55.0)	72 (68.6)	1.78 (1.13-2.81)	0.012
Captopril	173 (43.2)	65 (61.9)	2.13 (1.37-3.31)	< 0.001
Acetylsalicylic acid	198 (49.5)	74 (70.5)	2.43 (1.53-3.86)	< 0.001
Enoxaparin	191 (47.8)	62 (59.0)	1.57 (1.02-2.43)	0.025
Cefotaxime	180 (45.0)	52 (49.5)	1.19 (0.78-1.84)	0.408
Metaclopramide	185 (46.2)	55 (52.4)	1.27 (.83-1.96)	0.263
• Co-morbidity Score (Charlson Index)				
Low co-morbidity ≤ 2	174 (43.5)	14 (13.3)		
High co-morbidity ≥ 3	226 (56.5)	91 (86.7)	5.00 (2.75-9.08)	< 0.001
• Characteristics of the interaction				
Number of interactions per patient				
≤ 2	135 (33.7)	10 (9.6)		
≥ 3	265 (66.3)	95 (90.4)	4.40 (2.28-8.50)	< 0.001
• Time with the interaction				
Moderate (≥ 4 days)	332 (83.0)	46 (43.8)	10.41 (6.22-17.41)	< 0.001
Severe (≥ 4 days)	102 (25.5)	82 (78.1)	6.26 (3.93-9.97)	< 0.001

Table 4. Final model concerning the relationship between potential DDIs and discharge death.

Variables	OR	CI (95%)	p
• Patient characteristics			
- Age ≥ 75 years	6.90	3.27 - 14.53	< 0.001
- Stay ≥ 6 days in hospital	2.52	1.14 - 5.55	0.022
• Characteristics of the prescription			
- Having drugs with ≥ 6 ATC codes	5.63	2.71 - 11.70	< 0.001
- Charlson Index score (≥ 3)	2.69	1.31 - 5.52	0.007
- Presence of ≥ 3 interactions (moderate and/or severe)	4.12	1.82 - 9.31	0.001
- Duration of the moderate interaction (≥ 4 days)	5.37	2.86 - 10.05	0.001
- Duration of the severe interaction (≥ 4 days)	2.79	1.48 - 5.24	0.001

*Adjusted for age, number of prescriptions per day, and type of medication.

(furosemide/C03CA01 n = 72, 68.6% and captopril/C09AA01 n = 65, 61.9%), followed by antithrombotic agents such as acetylsalicylic acid (ASA)/B01AC06 (74; 70.5%), and those for the digestive system and metabolism such as metaclopramide/A03FA01 (55, 52.4%), among others. Of these patients, 91% had a high comorbidity score.

In exploring the relationship between potential DDIs and discharge due to death, various variables were individually considered by univariate analyses; the odds ratio (OR) for each variable is presented in table 3. A greater risk for discharge due to death was found to be associated with older age (OR = 9.25, CI 95% 4.81-17.81), hospitalization for more than six days (OR = 2.05, CI 95% 1.11-3.76), presenting three or more interactions (moderate and/or severe) (OR = 1.63 1.02-2.6), as well as an exposure time to the interaction greater than four days (OR = 1.67 1.46-1.91).

The probability of death was seven times greater among patients who presented six and more ATC codes, i.e. medications for different therapeutic functions. The patients who presented a severe interaction were three times more likely to die than patients who presented a moderate interaction. The medications employed for the cardiovascular system (code C) presented a greater risk of patient death during hospital stay (OR = 6.05, CI 95% 3.57-10.24); ASA (OR = 2.43, CI 95% 1.53-3.86) and the presence of a high comorbidity score (OR = 5.00, 2.75-9.08) had strong associations with discharge due to death. The adjusted ORs and 95% confidence intervals for the variables included in the final model are shown in table 4.

Age, duration of stay, number of ATC, a high comorbidity, the presence of three or more interactions and exposure time to serious interactions were each independently associated with discharge due to death. The collinearity between variables was ruled out by likelihood ratio test ($\chi^2 = 0.000$). The results of logistic regression model showed that 87.64% of the cases were correctly classified. The area under the ROC curve proved to be 0.854.

DISCUSSION

Frequency of potential DDIs in hospitalized elderly patients was 82.13%, of which 43.56% were severe and 38.57% were moderate in this work. These percentages suggest that there may be potential harm to patients that could be avoided. However, comparison of results from multiple studies is difficult due to the different methods utilized to classify potential DDIs, the characteristics of hospital care, and the type of medical service with which these studies were performed.

Potential DDIs are highly common according to our results when compared with results from the work by Nixdorf, *et al.,* who reported a frequency of potential DDIs of 25% in an emergency department,[9] Peral Aguirregoitia, *et al.,* reported a frequency of potential DDIs of 6.1% in a general population of a Medicine Department,[21] and Goldberg RM, *et al.,* found a frequency of potential DDIs of 50.4%.[8,22]

One work that has used the Micromedex system at the moment of hospital admission and discharge reported similar results found in the present study.[23] The high prevalence of potential DDIs carries adverse clinical consequences that could be avoided by the prescription of a different drug. For example, the most frequent moderate DDI in this work was caused by the ACE inhibitors and loop diuretics; their clinical relevance has been shown in previous studies because they involve severe hypotension and impaired renal function. This effect can be prevented by a reduction of the diuretic dose for three days before initiating

treatment with the ACE inhibitor, followed by renal and electrolyte monitoring.[24]

On the other hand, the most frequent severe DDI in our work was that generated by the combination of fluoroquinolones and antidiabetic agents. This combination can cause hypoglycemia or hyperglycemia, which could cause death;[25] this can be prevented if the blood glucose is closely monitored.[26] Due to the retrospective design of this research, it was not possible to determine whether preventive measures were taken.

ASA was the most frequently administered drug due to its multiple uses in our study (analgesic, antipyretic, and anticoagulant). It was used with ACE inhibitors (enalapril or captopril), and the combination, by direct action on glomerular filtration, could cause mild renal failure in elderly or dehydrated patients. Also may reduce the antihypertensive effect of the ACE Inhibitors by the inhibition of prostaglandins, the vasodilatory effect can cause death especially in patients with heart failure.[27-29] ASA in combination with loop diuretics (furosemide) could cause acute renal failure, especially in dehydrated patients. The synergistic effect of ASA and diclofenac can increase the risk gastrointestinal hemorrhages. Finally, ASA in combination with insulin may increase the hypoglycemic effect.[30] Due to the gravity of the possible adverse effects that consequently result from these interactions, medications must be managed with precaution and coadministration must be avoided in some cases.

Age, gender, polypharmacy, the type of medicine, and length of hospital stay were associated with discharge due to death; these were factors in previous studies reportedly associated with potential DDIs,[2,31,32] In fact, the association between discharges due to death with these factors continued to be significant even after adjusting for the number of medicines administered, comorbidity, and other factors.[2]

There are multiple studies in the literature that address the theme of potential DDIs; however, few of them have studied their clinical relevance, and even fewer address the death of the patient as a final result of the interaction. Contrary to the work by Klarin, *et al.*,[33] who did not find an association between the potential DDIs and mortality, we found an association between the type and number of potential DDIs and the duration of the interaction with the risk of discharge due to the death in hospitalized patients; although some differences between the studies may be due to the patient profile and the fact that them conducted a community-based study, such as a lower average number of medications per person and a less comorbidity by Charlson Index than the results observed in our research.

A community-based work by Hanlon, *et al.*,[12] reported no association between inappropriate prescriptions and mortality, although the number and severity of diseases and medications were different in that study population compared to those found among hospitalized patients.

In our study, we observed that the factors reportedly associated with the occurrence of a potential DDI also showed an association with discharge due to death in elderly patients. An example of such a factor was the length of hospital stay (OR: 4.06);[34] this result can be explained by the fact that with greater hospitalization time the patient receives a greater amount of drugs with a higher due to death include the severity of the disease and comorbidity, about this Klarin, *et al.*, reported a Charlson Index score of ≥ 3 (OR = 3.55) to be associated with mortality.[33] In our study, the association between length of hospital stay and mortality rate did not change when adjusted for the average number of daily prescriptions as well as for comorbidity. Thus, our results suggest that older age, a prolonged hospital stay, and the type and nature of the prescribed drug could be related to discharge due to death, independent of the comorbidity of the patient. However, this association should be interpreted with precaution since the clinical manifestations of potential DDIs were not evaluated. Nevertheless, given the growing rate of utilization of hospital services by the elderly, our results show the urgent need to consider Potential DDIs in routine clinical practice; in addition, guidelines are needed for conducting further studies to strengthen our results.

The main limitations of this research are the retrospective design and the use of medical charts for acquiring patients' clinical information. For these reasons, we must consider information bias caused by the lack of complete information in the clinical records; in addition, the clinical effect of the Potential DDIs were not evaluated, and we did not take into account the medical staff's recommended management for the interactions. However, we believe that these findings give rise to the development of longitudinal studies that permit the corroboration of these results. Others negative factors associated to mortality must be considered, such as disability, malnutrition, falls, frailty, cognitive impairment, among other geriatric syndromes.

CONCLUSIONS

This work shows that the occurrence of potential DDIs in the elderly population in the hospital environment is frequent, and potential DDIs may be

the cause of the discharges due to death of these patients. This work contributes to the epidemiological literature detailing potential DDIs and their harmful and undesirable effects. Discharge due to death after the hospitalization of elderly patients is directly related to the number of medications prescribed, the duration of the hospital stay, the type of interaction, and the exposure time, among other factors. Our results emphasize the importance, the development and implementation of training programs based on the application of the National System of Pharmacovigilance[35] for medical personnel may help to avoid interactions between potentially dangerous medications that put the lives of elderly patients at risk during hospitalization.

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