Validating a Trigger Tool for Detecting Adverse Drug Events in Elderly Patients With Multimorbidity (TRIGGER-CHRON)

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Purpose: The aims of the study were to evaluate the performance of an initial list developed to detect adverse drug events (ADEs) in elderly patients with multimorbidity in clinical practice, to explore the possibility of shortening the list, and to use this tool to study the incidence and characteristics of the ADEs among this population.

Methods: This observational study was conducted at 12 Spanish hospitals. A random sample of five charts from each hospital was selected weekly for retrospective review for a 12-week period. We included patients aged 65 years and older with multimorbidity, hospitalized more than 48 hours. Adverse drug events were detected using a list of 51 triggers previously selected by an expert panel by means of a modified Delphi method. The number of triggers identified and ADEs detected were recorded. The severity and preventability of the ADEs were evaluated. The positive predictive value (PPV) of each trigger was calculated and used to select the most efficient triggers.

Results: In 720 charts reviewed, 1430 positive triggers were identified that led to detect 215 ADEs in 178 patients (24.7%), of which 13% were serious. One hundred nineteen ADEs (55.3%) were preventable and mainly related to inadequate treatment monitoring and prescribing errors. Triggers with a PPV of 5% or less were eliminated, resulting in a final list of 32 triggers (TRIGGER-CHRON) with a PPV of 22.1%, which accounted for 98.9% of all ADEs detected and 98.6% of the preventable ADEs.

Conclusions: The shorter final validated TRIGGER-CHRON tool is an efficient list for identifying ADEs in elderly patients with multimorbidity, detecting ADEs in one-fourth of hospitalized patients in internal medicine or geriatric units.

Key Words: chronic patient, drug-related adverse effects and adverse reactions/diagnosis, multimorbidity, patient safety

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Patient safety data from all over the world indicate that the burden of medication-related avoidable harm is very high. For this reason, the World Health Organization (WHO) has launched its third global patient safety challenge, *Medication Without Harm*, underscoring that "*unsafe medication practices and medication errors are a leading cause of avoidable harm in health care systems across the world.*"[1] With this challenge, the WHO proposes to push forward and implement actions focused on improving medication safety and reducing the number of preventable adverse drug events (ADEs).

Polypharmacy is one of the key focus areas of this challenge. Currently, because of aging and increasing life expectancy, there are many more older patients who take multiple medications to treat more than one chronic disease. This intake has produced an increase in the likelihood of prescribing medication errors involving drug interactions, wrong dosages, etc, as well as patient-induced errors due to the difficulties inherent in keeping up with complex drug regimens.[2] Errors are also more frequent in the healthcare transitions, especially upon discharge from hospital to home.[3] The PRACtICe Study, carried out in the United Kingdom, designed to discover the nature of prescription errors in general practice during a 12-month period, found a rate of 30.1% of errors in patients who took five or more different drugs, a figure that increased along with the number of medications taken to a rate of 47% in patients who took 10 or more different drugs.[4] The number of drugs taken regularly is also the most frequently documented risk factor for serious ADEs, based on a systematic review of 26 studies including 85,212 patients.[5] It should be noted as well that older patients with multimorbidities are more likely to experience drug-related events and have higher ADE prevalence rates compared with other age groups.[6]

To make progress in improving medication safety and achieving the objective of reducing the number of errors for this challenge, health care organizations must have at their disposal an efficient, straightforward method to measure ADEs and to monitor the results of improvement interventions as they are implemented. Bearing in mind what has been stated previously, it would be very advantageous to have a special tool to detect ADEs in polymedicated older patients.

The trigger tool methodology was developed by the Institute for Healthcare Improvement as a low-resource option to detect adverse events at hospitals.[7] Trigger tools involve the application of various screening criteria to guide the medical review process in the identification of adverse events, making the process more efficient.[8] They may also be used concurrently, integrated into health information technology, to provide rapid, real-time identification of adverse events and enable timely interventions that can mitigate the adverse events detected.[9] Trigger tools seem to be the most efficient and cost-effective single method for detecting harm associated with health care, which is why numerous studies using the trigger method to measure ADE rates in health care organizations have been published.[10]

Various trigger tools are available from the Institute for Healthcare Improvement Global Trigger Tool to monitor overall levels of harm for hospitals[8] to specific sets of triggers developed for a particular purpose, in terms of identifying a specific type of event (e.g., drugs), clinical setting (e.g., mental health setting, nursing home, primary care), or group of patients (e.g., pediatric).[11–14]

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Considering the interest that exists in having available a set of triggers for detecting ADEs in elderly patients with multimorbidity, we developed a list for these patients based on existing triggers described in the literature and these triggers were evaluated by an expert panel for their appropriateness following a modified Delphi method.[15] This initial list included a total of 51 triggers organized into five modules.

The aims of the present study were to validate this initial list of triggers focused on elderly patients with multimorbidity in clinical practice, to explore the possibility of shortening the list in accordance with the results obtained, thus making the trigger tool more efficient, and to describe the incidence and characteristics of the ADEs detected using this tool with this population.

METHODS

This observational, retrospective study was conducted in 12 Spanish hospitals. The study protocol was authorized by the ethics committee of Clinical Research at the University Hospital Virgen del Rocío, located in Seville, Spain (coordinating hospital), and then again by the local ethics committees at each participating hospital, according to Spanish regulations.

The development of the set of triggers that were used in the study has been previously reported.[15] Briefly, 72 triggers identified through a detailed literature review were evaluated by an expert panel for appropriateness for in chronic patients using a modified Delphi method. The final list included a total of 51 triggers that were organized in the following five modules: 11 care module triggers, 10 antidotes/treatments, 11 medication concentrations, 18 abnormal laboratory values, and one emergency department trigger.

At each hospital, a weekly sample of five medical charts of patients discharged the week before from internal medicine or geriatric units was selected for review for a 12-week period (March 20 to June 11, 2017). Patients were eligible if they were chronic patients 65 years and older with multimorbiditiy whose hospitalization had been more than 48 hours. According to the WHO, multimorbidity was considered to be the presence of two or more chronic medical conditions in an individual.[16] Patients were excluded if they were in the hospital less than 48 hours, were hospitalized in other different clinical units of internal medicine or geriatrics, were receiving palliative care, or had been transferred in from other clinical units instead of the units under study (i.e., intensive care unit [ICU]). Charts for review were randomly selected in each hospital from the list of eligible patients generated from the patients discharged the week before using the randomization function found at https://www.random.org/sequences/.

We developed an instruction manual with standard processes and definitions for the triggers for guidance during the chart review and evaluation, and this was explained in detail at a meeting with all coordinators at each hospital. Several training exercises were also reviewed at this meeting. In addition, a practice pilot study was held (November 14 to 27, 2016) so that researchers at each hospital would have a chance to clear up any doubts they might have had regarding the methods and definitions using real cases, before beginning the actual study.

Selected charts were reviewed locally for the presence of triggers by a clinical pharmacist. The following sections of the charts were reviewed: medical progress notes, nursing flow sheets, medication orders, and laboratory data. Each identified trigger prompted an in-depth analysis of the chart to determine whether an associated ADE had occurred.

An electronic data collection tool was developed so that each hospital could record its data. The following variables from each chart were recorded: age, sex, number of chronic diseases and types of diseases, length of hospital stay, number of medications taken at home, number of medications administered during the hospital stay, number of doses administered, triggers identified, and ADEs detected. The severity of the ADEs was evaluated using of the National Coordinating Council for Medication Error Reporting and Prevention Index.[17] Only categories E to I were used, because these categories describe harm: category E (temporary harm to the patient requiring intervention), category F (temporary harm to the patient and requiring initial or prolonged hospitalization), category G (permanent patient harm), category H (intervention required to sustain life), and category I (patient death). Researchers determined whether or not the ADEs could have been prevented using Schumock and Thornton's preventability criteria adapted by our working group.[18,19] Whenever questions or discrepancies arose, the hospital physician responsible for the patient involved was contacted. In addition, preventable ADEs were analyzed according to the updated Spanish taxonomy of medication errors established by the Otero et al[20] to classify the type of errors associated with it. Once completed, the data from each hospital were posted onto the electronic data collection tool and sent for review by the principal investigators for consistency. All questions were directed to the responsible investigator at each hospital for resolution.

The positive predictive value (PPV) was calculated for each trigger (as the number of ADEs identified using this trigger divided by the number of times the trigger was identified in the charts). The PPV was also calculated for each of the modules and for the overall trigger tool. An ADE could have been identified by one or more triggers. Finally, after the analysis was complete, the triggers that came in with a higher rate than a preestablished cutoff of PPV of more than 5% were kept for inclusion in the final tool. This value was selected based on a study

TABLE 1. Patient Characteristics

	All Patients (n = 720)	Patients With ADEs (n = 178)	Patients Without ADEs (n = 542)	
Characteristic	**Median (Range)**	**Median (Range)**	**Median (Range)**	***P****
Age, y	83 (65–102)	84 (65–99)	83 (63–102)	$P = 0.043$
Length of stay, d	7 (2–67)	8 (2–53)	7 (2–67)	$P < 0.001$
Medications per patient				
Before admission	8 (2–20)	9 (1–19)	8 (0–20)	$P = 0.054$
At hospital	13 (3–42)	17 (7–37)	13 (3–42)	$P < 0.001$
Hospital doses per patient	106.5 (7–972)	150 (23–951)	95 (7–853)	$P < 0.001$
Pathologies per patient	6 (2–17)	6 (2–12)	6 (2–13)	$P = 0.158$

*P indicates that the cutoff P value used for statistical significance was $P \leq 0.05$.

conducted in a population with similar characteristics as the object population of our study.[14]

Descriptive statistics were calculated for patients and ADEs characteristics. Categorical data were summarized using frequency counts and percent. Continuous variables were presented as means with SD and median with range. A bivariate analysis of quantitative variables was carried out between the patients who had experienced an ADE and those who had not. The nonparametric Mann–Whitney *U* test was used to compare the quantitative variables.

RESULTS

A total of 720 randomly selected charts from the 12 hospitals were reviewed (60 charts per hospital). More than half represented women (55.4%). The median age was 83 years (range = 65–102) (Table 1). The number of medications taken per patient varied broadly, so that the median number of medications taken by patients before admission was 8 (range = 2–20) and the median number of medications given to these patients during their hospital stay was 13 (range = 3–42). The length of stay also varied broadly, with a median of 7 (range = 2–67), and a median of 165.5 for the number of hospital doses administered to the patients (range = 7–972). The median number of chronic illnesses per patient was 6 (range = 2–17). Table 2 lists the most frequently occurring diseases.

In the 720 charts, a total of 1430 positive triggers were identified, resulting in a mean rate of 1.98 ± 1.82 triggers per patient. After analyzing the triggers, a total of 215 ADEs were detected in 178 patients (24.7% of the 720 patients reviewed). Of the 178 patients with ADEs, 30 patients (16.9%) presented more than one ADE. The mean rate of ADEs was 29.9% per 100 admissions and 3.3 per 1000 medication doses received during hospitalization. The relevant characteristics of the patients with ADEs are listed in Table 1. These patients with ADEs experienced longer hospital stays than the patients without ADEs, and they were given more medications (17.1 ± 6.1 versus 13.5 ± 5.8) and a higher number of doses during their hospitalization (193.7 ± 166.7 versus 125.8 ± 110.4) and (10.3 ± 7.4 versus 8.5 ± 6.9).

TABLE 2. Most Frequently Occurring Diseases Among Patients

	All Patients (n = 720)	
Diseases	**n**	**(%)**
Hypertension	562	(78.1)
Dyslipidemia	347	(48.2)
Cardiac arrhythmia	292	(40.6)
Diabetes	289	(40.1)
Congestive heart failure	232	(32.2)
Kidney disease	202	(28.1)
Joint disease	194	(26.9)
Coronary heart disease	178	(24.7)
Dementia	170	(23.6)
Anemia	166	(23.1)
COPD	146	(20.3)
Benign prostatic hyperplasia	103	(14.3)
Brain stroke	100	(13.9)
Active solid or hematologic neoplasm	97	(13.5)
Obesity	95	(13.2)
Depression	90	(12.5)
Thyroid disease	91	(12.6)
Osteoporosis	77	(10.7)
Incontinence	75	(10.4)

COPD, Chronic obstructive pulmonary disease.

TABLE 3. Frequency of Errors Associated With the 119 Preventable ADEs

	Error* (n = 119)	
Type of Medication Error	**n**	**(%)**
Inadequate therapy monitoring	38	(31.4)
Wrong dose	38	(31.4)
Drug/dose omission	23	(19.0)
Wrong/inappropriate drug	6	(5.0)
Wrong frequency	3	(2.5)
Other types	13	(10.7)
Total	121	

*In some preventable ADEs, more than 1 type of error could be present in 1 ADE.

Most ADEs were associated with a National Coordinating Council for Medication Error Reporting and Prevention Index harm category of E (187/215, 87.0%). We found that 12.1% of ADEs were in category F, whereas only one ADE was classified as G and another as H. Regarding preventability, 119 of the 215 ADEs (55.3%) were deemed preventable. After analysis, a total of 121 types of errors were considered responsible for these 119 preventable ADEs. The most common type of errors was inadequate therapy monitoring (31.4%, defined as a failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy), wrong dosage (31.4%), and failure to prescribe a necessary drug (19.0%) (Table 3).

Table 4 A shows, for each trigger, the number of times it was identified after reviewing the charts, the number of ADEs detected, and their PPVs. Individual triggers varied widely in their yield of detection of ADEs. The median for PPVs was 12.7 with a range of 0.0% to 100%. Some frequently identified triggers had very low PPVs, as in the case of glomerular filtration rate (GFR) *of less than 35 mL/min per 1.73 m^2* (6.8%), which was identified 147 times, and only allowed for the detection of 10 ADEs. A wide variability was also found in the ADEs detected and the PPVs within the five modules. The *care module* and the *laboratory results module* were the modules that allowed for more ADEs to be identified.

Table 4 was divided into two blocks (Tables 4A and 4B) to summarize the outcomes of the triggers that had PPVs more than 5% and of all other triggers with PPVs less or equal than 5% (cut-off point). The triggers with PPVs more than 5% numbered 32 and were selected to become a definitive tool called TRIGGER-CHRON. The PPV of all the 51 triggers evaluated was 19.6% and the PPV of the TRIGGER-CHRON was 22.1%. These 32 triggers that were selected accounted for the 98.9% of all the ADEs and for 98.6% of the preventable ADEs. Furthermore, a "reduced TRIGGER-CHRON" set of 16 triggers was defined as a shorter option, which allowed to the detection of 89.6% of the ADEs and 86.7% of preventable ADEs.

DISCUSSION

Developing a set of triggers that will prove useful and appropriate for its intended purpose is a relevant topic in patient/medication safety.[9] Through an iterative approach involving a literature review of existing triggers and input from a Delphi panel

TABLE 4A. Prevalence of Triggers and ADEs and PPV of Triggers

Triggers selected = TRIGGER-CHRON	No. Triggers Found in the Charts	Total ADEs* (n = 215)			Preventable ADEs* (n = 119)		
		n	(%)	PPV, %	n	(%)	PPV, %
Module 1. Care triggers	**391**	**113**	**(40.51)**	**28.9**	**59**	**(39.07)**	**15.01**
Rash	11	2	(0.72)	18.2	1	(0.66)	9.1
New allergy	3	1	(0.36)	33.3	1	(0.66)	33.3
R Oversedation/lethargy	81	25	(8.96)	30.9	16	(10.6)	19.8
R Hypotension	82	28	(10.04)	34.1	10	(6.62)	12.2
R Transfusion or use of blood products	63	5	(1.79)	7.9	1	(0.66)	1.6
R Constipation	100	25	(8.96)	25	18	(11.92)	18
R Adverse reaction recorded	51	27	(9.68)	50	12	(7.95)	23.5
Module 2. Antidotes/treatments	**263**	**63**	**(22.59)**	**23.95**	**31**	**(20.52)**	**11.79**
R Vitamin K administration	30	6	(2.15)	20	5	(3.31)	16.7
Antihistamines IV	8	2	(0.72)	25	1	(0.66)	12.5
Flumazenil administration	5	3	(1.08)	60	3	(1.99)	60
Naloxone administration	4	2	(0.72)	50	2	(1.32)	50
R Antiemetic administration	63	8	(2.87)	12.7	2	(1.32)	3.17
R Haloperidol administration	84	5	(1.79)	5.9	4	(2.65)	4.8
R Abrupt cessation of medication	69	37	(13.26)	53.6	14	(9.27)	20.3
Module 3. Medication concentration triggers	**9**	**3**	**(1.08)**	**33.33**	**3**	**(1.98)**	**33.33**
Digoxin level > 2 ng/mL	8	2	(0.72)	25	2	(1.32)	25
Carbamazepine >13 µg/mL	1	1	(0.36)	100	1	(0.66)	100
Module 4. Laboratory results triggers	**575**	**96**	**(34.43)**	**16.69**	**55**	**(36.41)**	**9.57**
Clostridium difficile–positive stool	5	2	(0.72)	40	2	(1.32)	40
Serum glucose <50 mg/dL	16	2	(0.72)	12.5	1	(0.66)	6.3
R Serum glucose >110 mg/dL	182	38	(13.62)	25	23	(15.23)	12.7
R INR > 5	25	8	(2.87)	32	8	(5.30)	32
Rising BUN or serum creatinine > 2 times baseline*	11	1	(0.36)	9.1	0	(0)	0
R e GFR < 35 mL/min/1.73 m^2	147	10	(3.58)	6.8	4	(2.65)	2.7
R K > 6.0 mEq/L	26	7	(2.51)	26.9	6	(3.98)	23.1
R K < 2,9 mEq/L	30	9	(3.23)	30	4	(2.65)	13.3
R Na < 130 mEq/L	55	7	(2.51)	12.7	2	(1.32)	3.6
ALT >80 U/L and AST > 84 U/L	24	3	(1.08)	12.5	1	(0.66)	4.2
ALP > 350 U/L total bilirubin >4 mg/dL	8	1	(0.36)	12.5	0	(0)	0
CPK > 269 U/L	16	1	(0.36)	6.3	1	(0.66)	6.3
TSH < 0.34 µUI/L or T4 > 12 µg/dL	7	1	(0.36)	14.3	1	(0.66)	14.3
R HA1C > 6% and glucocorticoid	7	5	(1.79)	71.4	2	(1.32)	28.6
White blood cell <3000	16	1	(0.36)	6.3	0	(0)	0
Module 5. Emergency department triggers	**9**	**1**	**(0.36)**	**11.1**	**1**	**(0.66)**	**11.1**
Readmission to ED within 48 hours	9	1	(0.36)	11.1	1	(0.66)	11.1
Performance of the 16 "R" triggers (Reduced TRIGGER-CHRON)	1095	250	(89.61)	22.83	131	(86.75)	11.96
Subtotal of triggers selected	1247	276	(98.92)	22.13	149	(98.64)	11.95

Triggers included in TRIGGER-CHRON and in the reduced TRIGGER-CHRON.

Bold letter indicates the totals of the module.

*In several cases, 1 ADE was identified with more than 1 trigger.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, serum urea nitrogen; CPK, creatine phosphokinase; ED, emergency department; HA1C, glycated hemoglobin; INR, international normalized ratio; IV, intravenous; TSH, thyroid-stimulating hormone.

of experts, we developed an initial list of 51 triggers to identify ADES in elderly patients with multimorbidity,[15] a population that requires priority action to reduce incidents of avoidable harm caused by medication.[1] Applying this initial list in 12 hospitals led to the identification of at least one ADE per each four patients. However, a revision of these triggers based on the results obtained showed the necessity to shorten the initial list, and thus, 19 triggers were eliminated according to the cutoff previously established.

It should be noted that of the 19 triggers which were eliminated, eight triggers, all of which were from the *medication concentration* module, never occurred. This module, showing a very low sensitivity, only allowed for detecting 1.08% of all ADEs and

TABLE 4B. Prevalence of Triggers and ADEs and PPV of Triggers

Triggers Not Selected	No. Triggers Found in the Charts	Total ADEs* (n = 215)			Preventable ADEs* (n = 119)		
		n	(%)	PPV, %	n	(%)	PPV, %
Module 1. Care triggers	**60**	**1**	**(0.36)**	**1.67**	**1**	**(0.36)**	**1.67**
Falls	6	0	(0)	0	0	(0)	0
Acute dialysis	1	0	(0)	0	0	(0)	0
Unexpected medical or surgical emergency/sudden death	5	0	(0)	0	0	(0)	0
Readmission within 30 d	48	1	(0.36)	2.1	1	(0.66)	0.36
Module 2. Antidotes/treatments triggers	**82**	**1**	**(0.36)**	**1.22**	**1**	**(0.66)**	**1.22**
Risperidone administration	36	1	(0.36)	2.8	1	(0.66)	0.36
Long-term medications and classifications are at variance	46	0	(0)	0	0	(0)	0
Module 3. Medication concentration triggers	**3**	**0**	**(0)**	**0**	**0**	**(0)**	**0**
Lithium >1.5 mmol/L	0	0	(0)	NA	0	(0)	NA
Phenytoin >20 μg/mL	0	0	(0)	NA	0	(0)	NA
Phenobarbital >45 μg/mL	0	0	(0)	NA	0	(0)	NA
Valproic acid >120 μg/mL	0	0	(0)	NA	0	(0)	NA
Gentamicin/tobramycin levels: peak >10 μg/mL, trough >2 μg/mL	0	0	(0)	NA	0	(0)	NA
Amikacin levels: peak >30 μg/mL, trough 10 μg/mL	0	0	(0)	NA	0	(0)	NA
Vancomycin level: peak >40 μg/mL and trough 20 μg/mL	3	0	(0)	0	0	(0)	0
Cyclosporine >400 ng/L	0	0	(0)	NA	0	(0)	NA
Tacrolimus level > 20 ng/mL	0	0	(0)	NA	0	(0)	NA
Module 4. Laboratory results triggers	**38**	**1**	**(0.36)**	**2.63**	**0**	**(0)**	**0**
Hypercalcemia >10.5 mg/dL	2	0	(0)	0	0	(0)	0
Platelet count <50,000	5	0	(0)	0	0	(0)	0
Hemoglobin >12 g/dL	2	0	(0)	0	0	(0)	0
Decrease in hemoglobin or hematocrit > 25%	29	1	(0.36)	3.5	0	(0)	0
Subtotal triggers not selected	183	3	(1.08)	1.6	2	(1.32)	1.1
Total of all triggers	1430	279	(100)	19.5	151	(100)	10.6

Triggers not included in TRIGGER-CHRON

Bold letter indicates the totals of the module.

*In several cases, 1 ADE was identified with more than 1 trigger.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, serum urea nitrogen; CPK, creatine phosphokinase; HA1C, glycated hemoglobin; INR, international normalized ratio; NA, not applicable, R, triggers included in a reduced list; TSH, thyroid-stimulating hormone.

1.98% of preventable ADEs. We attribute this to the fact that the prevalence of ADEs that can be detected through these triggers is low, given that the use of some of these medications is currently quite limited (i.e., phenobarbital) and that, in general, the doses for these medications is adjusted for hospitalized patients as needed according to their concentrations. Another factor that may have contributed to these eight triggers not happening is that the study population was limited to patients hospitalized in internal medicine and geriatric units, and that these eight triggers might have turned out differently if they were applied in other settings, e.g., ICU.

Another 11 triggers that were found in the charts did not allow for identifying any ADE or only detected one ADE. For example, *falls* was found six times in the charts and no ADE was detected; *readmission within 30 days* was found 48 times and only allowed for detecting one ADE. All of this indicates the necessity of evaluating the set of triggers for use in real clinical practice.

The final TRIGGER-CHRON tool consists of 32 triggers, a number similar to other trigger tool lists for measuring ADEs in specific populations,[11,12] though more than on the general trigger tool for ADEs.[21] This tool could be reduced even more by establishing the cutoff at a higher PPV value and especially by also taking into account their sensitivity, i.e., the percentage of ADEs detected per trigger. Thus, only six triggers (*serum glucose > 110 mg/dL*, *abrupt cessation of medication*, *hypotension, adverse reaction recorded, oversedation/lethargy, and constipation*), all with a PPV of 25 or greater, allowing for the detection of 65.5% of all ADEs and 61.6% of preventable ADEs. If 10 more triggers were added (all the ones shown in Table 4 with an "R"), it would be possible to capture 89.6% of all ADEs and 86.8% of preventable ADEs. However, among these would not be included triggers having a low prevalence but a high PPV (i.e., *Flumazenil or Naloxone administration*) and that might provide relevant information regarding preventable harm. It was for this reason that we decided to define the final list with 32 triggers to increase the capacity to detect other less prevalent ADEs, bearing in mind the desire to implement these triggers into computer software linked to the patient electronic health record, which makes detection easier and also allows for identifying the ADE in real time during the clinical episode and thus allowing actionable interventions to prevent or mitigate the harm.[22] In addition, a reduced set of 16 triggers was defined as a shorter option for those situations in which a manual procedure of chart review is used and professionals do not wish to use the complete version. Finally, it should be noted that hospitals can customize the TRIGGER-CHRON according to their own objectives

and select the triggers that may be most useful at any given time for surveillance and for guiding system-level interventions such as those focused on identifying ADEs associated with a particular drug or drug group.[23]

To the best of our knowledge, this is the first study to report on the performance of a specific set of triggers focused on identifying ADEs in elderly patients with multimorbidity in a hospital setting. By applying this methodology, we found that 24.7% of these patients experienced an ADE while hospitalized, a figure that is consistent with that observed in recent studies using triggers[24,25] and greater than the incidence observed in previous studies.[26–28] This variability could be explained by the different methodology used, as well as by the different settings and study populations.

In our study, we were able to analyze in detail the ADEs at each hospital, thanks to collaboration among pharmacists and doctors, and discovered that more than half of the ADEs were preventable. We also found that the types of errors that had caused these preventable ADEs were prescribing and monitoring errors, as in other studies.[27–31] This was quite predictable, because the data were collected from medical charts, in which errors related to dispensing and administration are not commonly recorded and require other observational methods to make them all detectable.[32] All the information gathered in this study can be used to develop tailored interventions to reduce avoidable harm.

Finally, we found that the elderly patients who experienced ADEs received more medications during their hospitalization and had longer stays, as reported previously.[5,6,28] This, once again, shows that the number of medications taken is an important risk factor for ADEs and underscores the need to prioritize actions to benefit this especially vulnerable population. In this sense, a measure that could be useful would be to integrate the TRIGGER-CHRON into an active computer surveillance system to identify patients with risk of harm related to medications and to make interventions in real time when the information is available.

There are several limitations in the present study that are inherent to trigger tool methodology.[33] First, ADE detection was based solely on a retrospective review of the medical charts. Thus, outcomes depended on the quality of the documentation on the charts, which can vary among hospitals and among providers. Second, there is variability as well in the reviewers' interpretation of the triggers and ADEs, as well as in the preventability assessment of the ADEs. Although the professionals in charge at each hospital are experienced in the detection and analysis of ADEs and medication errors, we created a detailed instruction manual and a pilot study was carried out, some subjectivity surely remains that could affect outcomes. Third, the triggers are limited in number and scope, so that they may not capture all the ADEs. Still, one trigger explicitly included on this list, "*adverse reaction recorded*", allowed for detecting ADEs that were not identified through other triggers. Fourth, the incidence of ADEs in these patients might really be higher than that shown in the study population, because patients transferred to internal medicine or geriatric units from other clinical units (i.e., ICU) were excluded. Fifth, this study was performed applying the TRIGGER-CHRON tool in general Spanish hospitals, but there might be different results in other types of hospital belonging to other different geographical areas, with different clinical practices and/or health care systems. Furthermore, this study was carried out with inpatients and does not include information about events that occurred at outpatient settings except the ones related to readmissions.

Despite these limitations, our findings show that the shorter final validated TRIGGER-CHRON tool is an efficient list at identifying ADEs in elderly patients with multimorbidity hospitalized in internal medicine or geriatric units, because it allows for detecting ADEs in a quarter of patients. This tool could provide a standardized measure of harm-over-time in polymedicated older patients that can be used to determine the effect of medication safety improvement initiatives and concurrently provide real-time identification of ADEs, thereby enabling timely clinical interventions. Further studies are needed to prospectively explore the performance of this tool in both outpatient and long-term settings.

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