Routine use of the "ADE Scorecards", an application for automated ADE detection, in a general hospital

Emmanuel Chazard[a], Michel Luyckx[b], Jean-Baptiste Beuscart[c], Laurie Ferret[a], Régis Beuscart[a]

[a] *Public Health Department, Lille University Hospital; UDSL EA 2694; Univ Lille Nord de France; F-59000 Lille, France.*
[b] *Hospital Pharmacy, Lille University Hospital; UDSL EA 4481; Univ Lille Nord de France; F-59000 Lille, France.*
[c] *Geriatrics Department, Lille University Hospital; UDSL EA 2694; Univ Lille Nord de France; F-59000 Lille, France.*

Abstract

Retrospective detection of Adverse Drug Events (ADEs) is challenging, notably because ADEs result from complex interactions between many factors. Data mining techniques have recently emerged in the field of automated retrospective ADE detection. The "ADE Scorecards" are a research application based on data-mining that has been built in the frame of the PSIP European Project, and enables for automated potential ADE retrospective detection. The objective of this paper is to evaluate the use of the ADE Scorecards in real-life healthcare situation. For that purpose, the ADE Scorecards have been implemented in a French general hospital and have been used by the physicians and pharmacists during three years (corresponding to 73,000 inpatient stays). According to the results, 2% of the analyzed inpatient stays have a potential ADE with hyperkalemia, and 1% of them have a potential ADE with vitamin K antagonist overdose. In practice, the application, which was first designed to be a standalone web-based application for the physicians, has been used as a part of a more global quality improvement approach led by the pharmacists.

Keywords:

Adverse Drug Events, Adverse Drug Reactions, Data Mining, Data Reuse, Electronic Health Records.

Introduction

Adverse Drug Events (ADEs) can be defined as "injur(ies) due to medication management rather than the underlying condition of the patient" [1]. That definition emphasizes that ADEs are due to a combination of causes, including drugs (drug administration, dose variations, and drug discontinuations) and characteristics of the patient (such as age, diseases, renal and hepatic functions) [2]. That complexity explains why a certain skill is required to properly detect ADE cases.

Retrospective ADE detection consists in analyzing past hospital stays to discover cases where ADEs occurred. Several approaches have been developed in that field [3-4], and can be grouped into 2 categories: expert-operated methods and automated methods. The first ones mainly consist of retrospective medical chart reviews and reporting systems. The development of automated methods is more recent and tries to address the under-declaration and under-detection biases. Those methods are natural language processing of discharge summaries [5-8], and data mining of electronic health records (EHRs) [9].

Based on data mining, an application has been developed within the PSIP European Project (Patient Safety through Intelligent Procedures in medication). This application, named "ADE Scorecards" [10], is a surveillance tool that enables to automatically detect potential past ADE cases by highlighting the potential causes (drugs, biological context, demographics, etc) and the outcome. Those potential ADE cases can then be confirmed by experts and used for physicians' training. This application has been installed in five hospitals (2 Danish, 2 French and 1 Bulgarian) as a proof of concept. It has been routinely used by the physicians and pharmacists of a French general hospital during three years.

The objective of this paper is to present the application and show the results of its use in real-life situation.

Materials and Methods

EHRs from the Denain General Hospital

A structured description of past hospital stays is automatically extracted from the EHRs of the Denain General Hospital, in the North of France. Those records fit a data model that has been designed previously [11], and only uses routinely-collected data: no additional data has to be specifically recorded. The data model includes medical and administrative information (e.g. age, gender, admission date), diagnoses (ICD10 codes), medical procedures, drugs administered daily to the patient (ATC codes), laboratory results (IUPAC codes), and free-text records anonymized using the FASDIM procedure [12].

Adverse Drug Events detection rules

The knowledge about ADEs is generally described using ADE detection rules. An ADE detection rule is made of one or several Boolean conditions that may lead to an outcome, with a given probability, such as C_1 & ... & $C_k \rightarrow O$. This is a simplified notation, as in addition the rule implicitly requires that time constraints are respected: the condition must precede the outcome, and still be active when the outcome occurs. That representation is widely used either for prospective ADE prevention or retrospective ADE detection [13]. In this work we use a set of 236 rules that have been discovered in a previous work by data mining of EHRs [9]. In that work, routinely-collected inpatient data have been used to identify potential outcomes. Then, by mean of data-mining techniques (such as decision trees and association rules), conditions statistically associated have been identified. Finally, the rules have been

filtered, reorganized and validated by pharmacology experts. Those rules involve 1 to 4 conditions (demographic characteristics, drug administrations or discontinuations, laboratory results, or diagnoses) and an outcome that can be detected in the data (e.g. "Hyperkalemia", "International Normalized Ratio elevation", etc.). The rules include 56 kinds of outcomes. They are described as a set of structured XML files, including:

- mappings that enable to transform the raw data into Boolean variables with temporal attributes,
- the set of rules,
- a lexicon for automated translation into English, French, Danish or Bulgarian, and
- a set of free-text explanations, that explain each rule and provide with bibliographic references in each language.

The ADE Scorecards, a retrospective ADE detection tool

The ADE Scorecards are a web-based application that enables to detect and display potential past ADE cases in a user-friendly interface. The process relies on two steps (Figure 1).

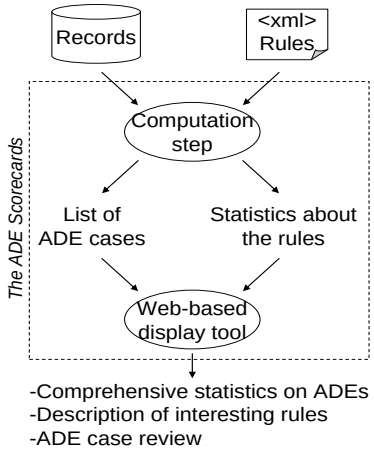

Figure 1 – The 2 parts of the ADE Scorecards

Rule: $C_1 \cap ... \cap C_k \rightarrow O$

Time constraints:

For $(C_1 \cap ... \cap C_k)$: all the conditions are present in the same time (they can start at different times)

For $(O \cap C_1 \cap ... \cap C_k)$: the same as above, and all the conditions are present before the outcome starts.

Support: $Sup = P(O \cap C_1 \cap ... \cap C_k)$

Confidence: $Conf = P(O / C_1 \cap ... \cap C_k)$

Risk ratio: $RR = \frac{P(O / C_1 \cap ... \cap C_k)}{P(O / \overline{(C_1 \cap ... \cap C_k)})}$

P value: p value of the Fisher's exact test for independency between the outcome *O* and the set of conditions $(C_1 \cap ... \cap C_k)$

Delay: median delay between $Time(C_1 \cap ... \cap C_k)$ and $Time(O)$ (when both events occur).

Figure 2 – Contextualized statistics (underlined)

The *computation step* consists in running the ADE detection rules onto the inpatient stays that are extracted from the EHRs. Several contextualized statistics are computed for each rule in each medical department (Figure 2). They enable a contextualized behavior of the application. Indeed, previous works have demonstrated the need for such contextualization in the field of ADE detection [14]. As a result of that first step, several inpatient stays are flagged as "potential ADEs" (those cases are not always real ADEs, they have to be confirmed).

The second step, *web-based display tool*, consists in displaying the potential ADE cases, the related ADE detection rules, and statistics. For that purpose, a web-based application has been developed using a Human-centered design process [15]. It preserves the anonymity of the patients. Finally, the users are provided with contextualized information: the potential ADE cases are detected in their medical unit, the statistics are contextualized, and only the ADE detection rules that are useful in their medical unit are displayed. A free demonstration of the application is available on the Web [16]. Finally, a case facility enables to visualize each potential ADE case, enabling the physicians to making their own opinion on the detected cases.

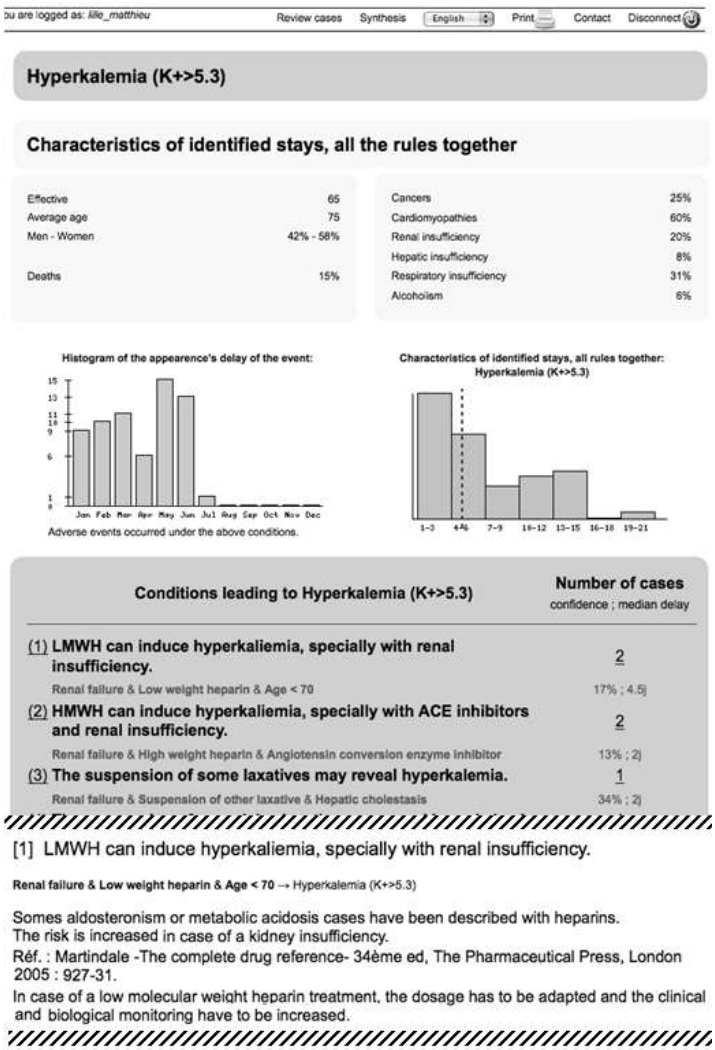

Figure 3 – Scorecard of potential ADEs with hyperkalemia (hatched lines denote a truncation of the screenshot)

Quantitative observation of the application

The data are analyzed from January 2007 to August 2012. Some statistics are computed to describe the patients and their medical background, especially the characteristics that are known to have a strong interference with medications. Comparisons are performed using Chi-2 tests and Student's t-tests with a 5% alpha risk. Confidence intervals are computed with a 5% alpha risk.

The number of potential ADE cases detected by the application is computed in the medical departments and year after year. A focus is made over the most frequent outcomes:

- Hyperkalemia: it is defined as K^+>5.5mmol/l in this case. This ionic trouble may induce lethal cardiac rhythm troubles.
- INR increase: it is defined as INR>5 in this case (INR=international normalized ratio of the prothombin time). Such a disorder could induce a severe hemorrhage. A frequent cause is a VKA overdose or a VKA biological availability increase (VKA=vitamin K antagonists).

Qualitative preliminary evaluation of the use of the application in real-life

The daily use of the Scorecards is observed from January 2010 to December 2012 by a human-factors specialist and a pharmacist. They observe how the application is used in practice by analyzing log files, interviewing users and analyzing staff meetings that use the outputs of the tool. This observation is the preliminary study of a more complete and structured evaluation.

Results

Description of the inpatient stay database

The number of inpatient stays analyzed is in Table 2. Only the inpatient stays that present the following characteristics are analyzed: there is at least one drug administration, the patient is hospitalized during at least 2 days, and the patient is hospitalized in a medical department where the ADE Scorecards are implemented. The general characteristics of the inpatient stays are displayed in Table 1. Those characteristics are compared between the medical departments in Table 3.

Table 1 – Description of the inpatients stays analyzed

Parameter	Estimated value
General characteristics	
Age (years)	60.2
Length of stay (days)	8.01
Proportion of men	40.8%
Abnormal laboratory results	
INR increase	2.46%
Hyperkalemia	5.43%
Chronic diseases (ICD10 codes)	
Renal insufficiency	2.02%
Hepatic insufficiency	4.90%
Administered drugs	
VKA	8.34%
Diuretics	23.3%
Main medical department	
Cardiology	24.4%
Geriatrics	3.75%
Gynecology Obstetrics	10.0%
Internal medicine	18.4%
Pneumology	15.8%
Surgery	27.7%

Table 2 – Number of inpatient stays and stays analyzed

Year	Total number of stays	Number of stays analyzed
2007	10,244	6,084
2008	11,338	6,271
2009	12,469	6,215
2010	14,747	6,490
2011	15,042	6,274
2012 (Jan-Aug)	9,996	4,301
TOTAL	73,836	35,635

Table 3 – Comparison of the inpatients stays between medical departments (p<0.001 in each line of the table)

Department	Cardiology	Geriatrics	Gyn. Obs.	Int. med.	Pneumo.	Surgery
Age (years)	67.6	82.4	28.0	69.7	67.8	57.6
Length of stay (days)	8.19	11.6	6.56	10.5	11.8	8.42
Men	42.8%	28.8%	0.00%	39.4%	63.2%	37.8%
Renal insufficiency	3.04%	4.83%	0.04%	4.20%	2.04%	0.60%
Hepatic insufficiency	13.7%	2.42%	0.04%	6.26%	2.34%	1.47%
VKA	15.5%	12.9%	0.00%	13.7%	14.8%	1.67%
Diuretics	41.1%	30.1%	0.00%	31.6%	35.4%	12.9%

Irrespectively from being ADEs or not, many abnormal laboratory results are observed during the hospitalizations as defined in the "Material and Methods" section. Their incidence rate is displayed in Table 4.

Table 4 – Proportion of stays with an abnormal laboratory result detected during the hospitalization (being ADEs or not)

Parameter	Estimated value
INR increase	2.46% [2.30% ; 2.62%]
Hyperkalemia	5.43% [5.19% ; 5.67%]

Estimated number of ADEs

This section presents the number of potential ADE cases detected by the ADE Scorecards (without expert validation).

Table 5 displays the number and proportion of potential ADE cases with INR increase year after year (see also Figure 4). Those proportions are detailed by medical department in Table 6.

Table 5 – Potential ADE cases with INR increase (2012: from January to August)*

Year	Number	Proportion
2007	67	1.10% [0.84%;1.36%]
2008	60	0.96% [0.72%;1.20%]
2009	71	1.14% [0.88%;1.41%]
2010	49	0.76% [0.54%;0.97%]
2011	61	0.97% [0.73%;1.22%]
2012*	45	1.05% [0.74%;1.35%]
TOTAL	*353*	*0.99% [0.89%;1.09%]*

Table 6 – Potential ADE cases with INR increase by medical department (comparison: p<0.001)

Department	Proportion
Cardiology	1.36% [1.07%;1.65%]
Geriatrics	0.00% [0.00%;0.00%]
Gynecology Obstetrics	0.00% [0.00%;0.00%]
Internal medicine	1.63% [1.27%;1.99%]
Pneumology	2.12% [1.67%;2.56%]
Surgery	0.14% [0.05%;0.23%]

Table 7 displays the number and proportion of potential ADE cases with hyperkalemia year after year (see also Figure 4). Those proportions are detailed by medical department in Table 8.

Table 7 – Potential ADE cases with Hyperkalemia (2012: from January to August)*

Year	Number	Proportion
2007	145	2.38% [2.00%;2.77%]
2008	146	2.33% [1.95%;2.70%]
2009	125	2.01% [1.66%;2.36%]
2010	108	1.66% [1.35%;1.98%]
2011	120	1.91% [1.57%;2.25%]
2012*	81	1.88% [1.48%;2.29%]
TOTAL	*725*	*2.03% [1.89%;2.18%]*

Table 8 – Potential ADE cases with Hyperkalemia by medical department (comparison: p<0.001)

Department	Proportion
Cardiology	2.65% [2.25%;3.05%]
Geriatrics	3.36% [2.22%;4.51%]
Gynecology Obstetrics	0.00% [0.00%;0.00%]
Internal medicine	2.68% [2.22%;3.14%]
Pneumology	2.77% [2.26%;3.27%]
Surgery	0.88% [0.66%;1.10%]

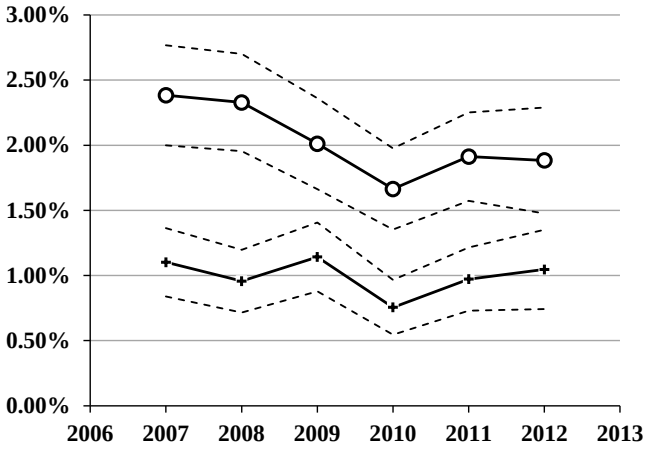

Figure 4 – incidence rates of potential ADEs ("+":INR increase; "o": Hyperkalemia; "---": 95% confidence intervals)

Qualitative preliminary evaluation

The ADE Scorecards are routinely used by two ways. Some of the physicians or head nurses use to connect monthly on the application to view the statistics and review some cases. But the most important use is made by the pharmacists of the hospital. Every month in every department, the pharmacists use to plan a meeting with all the physicians. Since the ADE Scorecards are installed, some interesting cases detected by the application are used to support the discussion. The pharmacists report that, formerly, their recommendations could sometimes be perceived as "too theoretical". By means of the ADE Scorecards, they can now support their recommendations with visual displaying of real ADE cases from the department they meet. Moreover, the ADE Scorecards are able to detect complex pharmacokinetic drug interactions that are rarely known and that were not discussed with the physicians formerly. According to the users of the Scorecards, about half the detected cases are real ADE cases with a cause-to-effect relationship between the potential causes highlighted by the application and the outcome. According to them, this ratio is sufficient to use it as a support tool for morbidity and mortality reviews, after an expert filtering.

Discussion

Initially designed in a research project, the ADE Scorecards have demonstrated after three years of daily use that they could also support real-life healthcare. The application enables to detect past ADE cases and highlights the causal conditions that are linked with some outcomes. It also enables to compute longitudinal statistics about ADEs.

In this study we estimate a 2% incidence rate of ADEs with hyperkalemia and a 1% incidence rate of ADEs with INR increase. Those figures, provided for two specific outcomes, are consistent with the literature. According to the literature, ADEs occur in 2.4 to 5.2 per 100 hospitalized adult patients [17-21]. In [22], 2.8 ADEs occur for 100 patients*days, this could correspond to 5-10% of the stays.

However, the incidence rates that are displayed in this study are related to *potential* ADEs and not *confirmed* ADEs. The ADE cases should be validated by means of an expert review. The qualitative evaluation suggests that the accuracy of the detection should be around 50%. A quantitative expert-operated review performed on a limited sample showed previously a precision (positive predictive value) of 52% in the field of hyperkalemia [9]. A more complete quantitative evaluation is still in progress: it consists in a case review (detected and undetected cases) performed by pharmacology experts.

The curves on Figure 4 suggest a small decrease of the ADE incidence rates of Hyperkalemia along the observation period. As the patients may differ from a year to another, a simple statistical comparison of proportions would not be sufficient. A more complete study is also in progress, in order to adjust incidence rates with the patients' medical background, by means of propensity scores.

The application was initially designed for a wide use by the physicians as a standalone tool. The qualitative evaluation suggests that the ADE Scorecards are more likely to be used as a support to a more global quality improvement approach, leaded by pharmacists. For instance, the ADE Scorecards enable to quickly find ADE cases, and those cases -as well as their user-friendly scrollable representations- are easy to validate or not, and to use in morbidity and mortality reviews. The quali-

tative evaluation that is still in progress principally aims at highlighting usability lacks and suggesting improvements of the tool.

Conclusion

The ADE Scorecards have demonstrated they could be used in real-life healthcare, especially as a support to more traditional quality improvement approaches. Complementary studies must be led to compute the precision of the ADE detection, and to assess whether the use of the application is associated with a change in the ADE incidence rates.

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Address for correspondence

Corresponding Author: Emmanuel Chazard; Clinique de Santé Publique, CHRU de Lille, 150 rue Yersin, 59037 Lille Cedex, France; emmanuel.chazard@univ-lille2.fr