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ORIGINAL REPORT

A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database

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ABSTRACT

Purpose Quantitative analytic methods are being increasingly used in postmarketing surveillance. However, currently existing methods are limited to spontaneous reporting data and are inapplicable to hospital electronic medical record (EMR) data. The principal objectives of this study were to propose a novel algorithm for detecting the signals of adverse drug reactions using EMR data focused on laboratory abnormalities after treatment with medication, and to evaluate the potential use of this method as a signal detection tool.

Methods We developed an algorithm referred to as the Comparison on Extreme Laboratory Test results, which takes an extreme representative value pair according to the types of laboratory abnormalities on the basis of each patient's medication point. We used 10 years' EMR data from a tertiary teaching hospital, containing 32 033 710 prescriptions and 115 241 147 laboratory tests for 530 829 individual patients. Ten drugs were selected randomly for analysis, and 51 laboratory values were matched. The sensitivity, specificity, positive predictive value, and negative predictive value of the algorithm were calculated.

Results The mean number of detected laboratory abnormality signals for each drug was 27 (±7.5). The sensitivity, specificity, positive predictive value, and negative predictive value of the algorithm were 64 – 100%, 22 – 76%, 22 – 75%, and 54 – 100%, respectively.

Conclusions The results of this study demonstrated that the Comparison on Extreme Laboratory Test results algorithm described herein was extremely effective in detecting the signals characteristic of adverse drug reactions. This algorithm can be regarded as a useful signal detection tool, which can be routinely applied to EMR data. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug event; postmarketing drug surveillance; pharmacovigilance; electronic medical record

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INTRODUCTION

Signal detection of adverse drug reaction (ADR) in postmarketing surveillance (PMS) has predominantly entailed observations and analyses of spontaneous reports by expert clinical reviewers. Quantitative methods are, however, being increasingly used for analysis in such situations, primarily because large clinical databases are capable of broader analyses even than large groups of clinical reviewers.[1] Representative analytic methods include relative reporting, proportional reporting rate ratio, reporting odds ratio, Bayesian Confidence Propagation Neural Network, and Multi-item Gamma-Poisson-Shrinker.[1,2] The algorithm generally referred to as "disproportionality analysis (DA)" basically uses the ratio of observed drug–event combinations and the drug–event combinations expected by pure chance. DA-based analytical methods have come to be considered the best quantitative screening methods for the detection of unknown or rare ADRs, and are regarded as an effective supplement to qualitative signal detection strategies.[1] However, the use of spontaneous reports as a principal data source for DA also raises some limitations of the spontaneous reports themselves, including the

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lack of denominator data of user populations and drug exposure, as well as the issue of significant underreporting.[2–6] Additional thresholding for disproportionality or unexpectedness notably requires individual, and occasionally arbitrary, decisions.

Previous attempts have been made to use other health care data for PMS, such as randomized clinical trial data sets,[7] claim databases,[8,9] or electronic patient records.[5,10] The global quantity of clinical information is rapidly increasing with increasing adoption of electronic medical records (EMRs). The EMR data have potential strengths, including sufficient sample size, population basis, relative inexpensiveness, and no possibility of recall or interviewer bias.[11] Inpatient EMR data, in particular, may potentially provide accurate diagnoses, accurate laboratory and radiology results, drug dosage and administration time, and readily detectable events during hospitalization.[11] However, because of the logical simplicity of DA, losses in the rich clinical context of the raw data are inevitable, even with full EMR data.

Drug effects are reflected to a considerable degree in clinical laboratory results.[12–14] Several pharmacoepidemiologic studies have linked clinical laboratory tests and drug exposure in large databases.[15–26] However, these studies have been, generally, manual rather than automated processes, as they depend on methods or systems that find individual cases that satisfy predefined laboratory conditions.

No reports have yet been conducted to determine whether or not an automated database-driven approach, analyzing the drug–laboratory events of EMR databases, might prove efficient in rapid ADR signal identification. The primary objectives of this study were to devise a novel algorithm for detecting ADR signals using an EMR database focused on laboratory abnormalities after treatment with medication, and to evaluate the potential use of this method as a signal detection tool.

METHODS

The novel Comparison on Extreme Laboratory Test results algorithm

The basic objective of the Comparison on Extreme Laboratory Test results (CERT) algorithm was to select laboratory abnormalities among all the possible laboratory results after the administration of medication during each patient's hospitalization period. That is, the abnormal laboratory values are used as a surrogate for an adverse drug event (ADE).

The CERT algorithm combines both (i) comparison between extreme laboratory results prior to medication and after medication during hospitalization and (ii) comparison between the counts of abnormal laboratory results prior to and after medication during hospitalization (Figure 1). Therefore, the CERT algorithm can be regarded as a quasi-experimental method, specifically a "one group pre–post test design" method. Use of the same medication before admission was not considered in the algorithm. The sequential results of a repeated laboratory test of a patient over the duration of his or her hospitalization were divided into laboratory tests prior to and after the first administration of the subject drug during hospitalization.

To select a representative laboratory value, the extreme value (minimum or maximum) among multiple laboratory values was selected for each premedication and postmedication laboratory test. The minimum or maximum value was selected as the extreme, according to the laboratory abnormality type. For hyper-type laboratory abnormalities such as elevated liver enzyme, the maximum value pair was selected. For hypo-type laboratory abnormalities such as neutropenia, the minimum value pair was selected. When both increases and reductions in a laboratory test were relevant to ADRs, such as prothrombin time, both hyper- and hypo-type laboratory abnormalities were included.

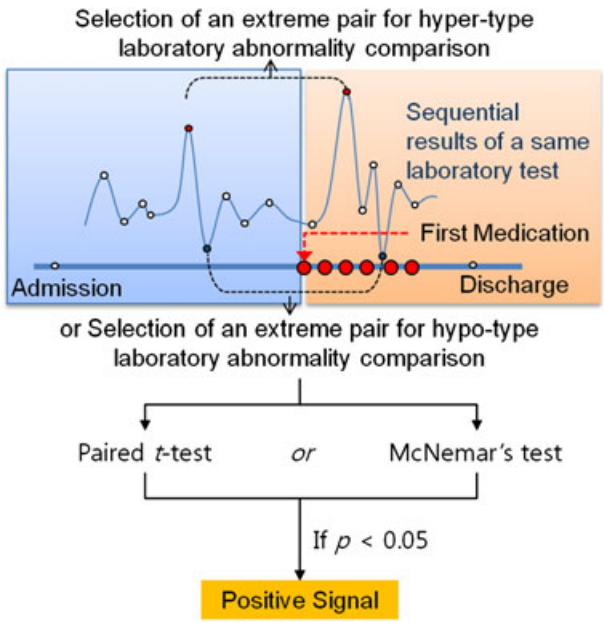

Figure 1. Comparison on Extreme Laboratory Test results algorithm. An extreme value pair such as the minimum or maximum value depending on the types of laboratory abnormalities was selected as a representative value for each patient. If either the result of the paired *t*-test or the McNemar's test is statistically significant ($p < 0.05$), the drug–laboratory abnormality pair was regarded as a positive signal

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Two groups of the extreme laboratory results—"prior to" and "after" medication were compared using a paired *t*-test for each drug set used. The same extreme pairs were used to compare the differences in the counts of abnormal laboratory test results prior to and after medication, via McNemar's test. Laboratory test results that fell below or above the reference range were regarded as abnormal results. When either the paired *t*-test or the McNemar's test was significant at a confidence interval of 95% ($p < 0.05$), the drug–laboratory abnormality pair was assigned as a positive signal.

Data source

We used the inpatient EMR database of a tertiary teaching hospital, Ajou University Hospital, in Korea. Since its opening in 1994, the Ajou University Hospital has expanded to accommodate 1030 patient beds, as well as other facilities including 92 intensive care units, 18 operating rooms, and state-of-the-art medical equipment. The hospital's information system allows for a patient's history and physician's notes to be digitally recorded and instantaneously available via our network to all patient departments, thus facilitating top quality medical service. All of the data were deidentified in an effort to protect patients' privacy and confidentiality. All protocols of this study were reviewed and approved by the Ajou University Hospital institutional review board.

The study database included information for admission, discharge, drug prescription, and laboratory test results from 1 January 2000 to 31 March 2010. The database contained a total of 32 033 710 prescriptions and 115 241 147 laboratory tests from 1 011 055 hospitalizations for 530 829 individual patients (Figure 2A).

Selection of target drugs

Ten drugs were randomly chosen for analysis among the 1265 drugs used in the hospital. These included seven non-oncologic drugs (including ciprofloxacin, clopidogrel, ketorolac, levofloxacin, ranitidine, rosuvastatin, and valproic acid) and three oncologic drugs (etoposide, fluorouracil, and methotrexate) (Figure 2B).

Selection of target laboratory results

To evaluate the algorithm, a great deal of accurate data on ADRs will first be required. However, currently, no proven gold standard exists with regard to ADRs. In this study, previously identified and published known ADEs were regarded and treated as a gold standard. We retrieved the known ADEs of the 10 selected drugs that could be relevant to laboratory abnormalities using the 2010 UpToDate® Drug Information Database (UpToDate Inc., Waltham, MA, USA), or UpToDate, as a reference literature source on 1 March 2010. It provides comprehensive lists of ADEs to determine whether or not the detected laboratory abnormalities had been previously published. However, ADEs are relevant to a variety of concepts: disease, symptoms, signs, syndromes, laboratory abnormalities, etc. ADEs are heterogeneous and non-explicit in nature. By way of contrast, the results of CERT algorithm analysis are represented solely as laboratory abnormalities. As they cannot be compared directly, a mapping system is required to compare the reported ADEs and detected laboratory abnormalities to evaluate the CERT algorithm. Therefore, we developed a mapping table linking known ADEs and detected laboratory abnormalities, as follows. The mapping table included 56 ADEs from UpToDate for the 10 drugs, and the laboratory abnormalities detected by the CERT algorithms were listed. The primary mapping between them was conducted by a surgical pathologist (R. W. Park). In the first round of consensus, the primary mapping table was evaluated independently by a hematologist (S. Y. Kang) and a nephrologist (I. W. Park), and rated as "correct or require minor modifications" or "require major modifications." After the first round of consensus, it was modified by adopting each evaluator's comments. The second consensus round was conducted using a modified table. If two evaluators continued to hold different opinions after the second round, the three physicians gathered to discuss the case and come to an agreement. The degree of inter-observer agreement was excellent ($\kappa = 0.95$; $p < 0.001$) after any disagreements were resolved by consensus. Connections with discrepancy even after second consensus were "anemia—total iron binding capacity increased" and "granulocytopenia—lymphocyte increased." The three participating physicians agreed to eradicate these from the mapping table, because of the ambiguous nature of the relationship of the connections. Among the 101 laboratory tests available in the data, 41 laboratory tests, all of which appear at least once in the ADR mapping table described above, were selected for evaluation. Consequently, from the 41 laboratory tests, 51 laboratory abnormalities were categorized by type and selected as target laboratory results (Figure 2D and Table 1).

Validation of Comparison on Extreme Laboratory Test results algorithm

The known ADEs for 10 drugs in the mapping table were adopted as the gold standards for the ADR of

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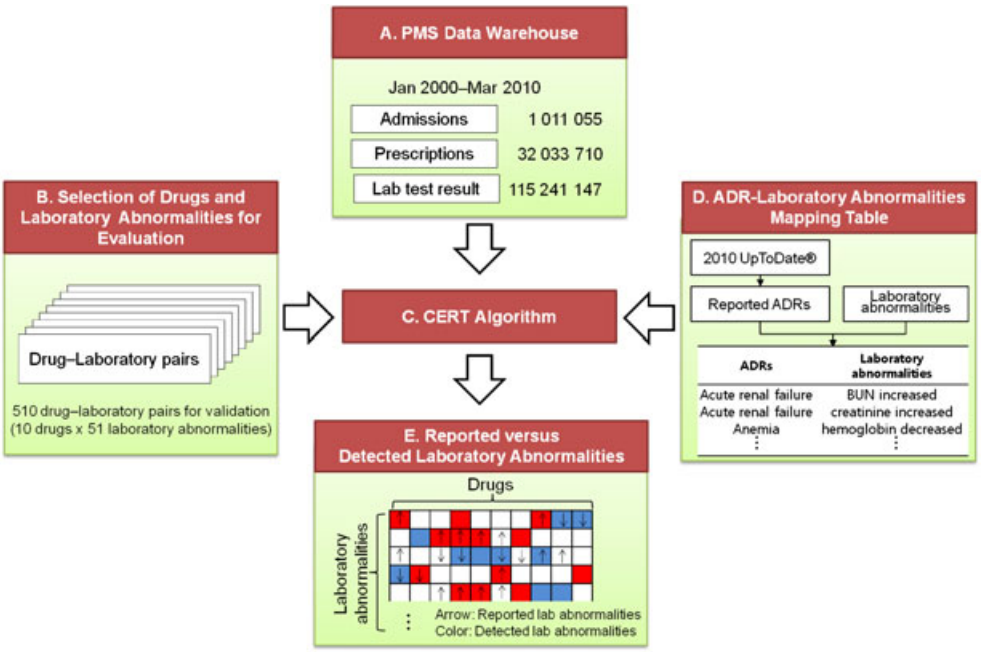

Figure 2. Validation of Comparison on Extreme Laboratory Test results (CERT) algorithm. (A) A postmarketing surveillance (PMS) data warehouse was constructed from a 10-year electronic medical record database of a tertiary teaching hospital. (B) A total of 510 unique drug–laboratory test pairs were prepared. (C) CERT algorithm detected statistically significant signals. (D) Adverse drug reactions (ADRs), which could be represented as laboratory abnormalities, for the selected 10 drugs were retrieved from the 2010 UpToDate Drug Information Database. A mapping table linking known ADRs to corresponding laboratory abnormalities was created. (E) The drug–event pairs (A) were evaluated via the CERT algorithm (C). BUN, blood urea nitrogen

each drug. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the CERT algorithm were calculated for the drugs in the aggregate, as well as each drug individually, as the formula shown in Figure 3. When we calculate sensitivity and specificity, previously known ADEs of a drug were compared with the ADEs converted from the laboratory abnormalities detected by CERT. For the calculation of PPV and NPV, laboratory abnormalities detected by CERT were compared with the laboratory abnormalities converted from previously known ADEs. One ADE was converted into one or more laboratory abnormalities and vice versa (Supplementary Table 1).

We also compared the performance of the CERT algorithm for non-oncology drugs with its performance for oncology drugs.

Software tools used

In implementing the CERT algorithm and EMR data processing system, Eclipse 3.2.2 (IBM, Riverton, NJ, USA) tools for JAVA programming and MS-SQL 2000 (Microsoft, Redmond, WA, USA) were used as a database management system. The R package (R Development Core Team, Vienna, Austria) was incorporated into the system for statistical analysis.

RESULTS

The CERT algorithm requires patients who were prescribed the target drug at least once and had generated one or more target laboratory results prior to and after the administration of the target drug during the same hospitalization period in the study database. There were 16 706 cases in which ciprofloxacin was used, along with 19 188 cases of clopidogrel, 82 273 cases of ketorolac, 9059 cases of levofloxacin, 68 995 cases of ranitidine, 4811 cases of rosuvastatin, 11 523 cases of valproic acid, 1466 cases of etoposide, 11 217 cases of fluorouracil, and 1576 cases of methotrexate (Table 2).

The matrix of the previously known and detected laboratory abnormalities for 510 unique drug–laboratory abnormality pairs was generated using CERT (Figure 4). The CERT algorithm detected 269 signals for 10 drugs. Pairs detected by CERT corresponded with previously well-known drug-induced adverse events in a substantial number of drug–ADE pairs. For instance, the association between ciprofloxacin and acute liver failure or serious liver injury has been widely established.[27,28] The results of the CERT algorithm suggested an association between ciprofloxacin and liver-related laboratory abnormalities. The liver-related laboratory

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Table 1. Forty-one laboratory tests and 51 laboratory abnormalities

Laboratory test name	Laboratory test abnormality
Activated partial thromboplastin time	Increased activated partial thromboplastin time
	Decreased activated partial thromboplastin time
Alanine transaminase	Increased alanine transaminase
Alkaline phosphatase	Increased alkaline phosphatase
Ammonemia	Increased ammonemia
Amylase	Increased amylase
Aspartate transaminase	Increased aspartate transaminase
Basophil	Decreased basophil count
Blood urea nitrogen	Increased blood urea nitrogen
Cholesterol	Increased cholesterol
Creatine kinase	Increased creatine kinase
Creatinine	Increased creatinine
Direct bilirubin	Increased direct bilirubin
Eosinophil	Increased eosinophil count
	Decreased eosinophil count
Fibrinogen	Decreased fibrinogen
Free thyroxine	Increased free thyroxine
	Decreased free thyroxine
Gamma-glutamyl transpeptidase	Increased gamma-glutamyl transpeptidase
Glucose	Increased glucose
	Decreased glucose
Hematocrit	Decreased hematocrit
Hemoglobin	Increased hemoglobin
	Decreased hemoglobin
Lactate dehydrogenase	Increased lactate dehydrogenase
Low-density lipoprotein cholesterol	Increased low-density lipoprotein cholesterol
Lipase	Increased lipase
Lymphocyte	Increased lymphocyte
Myoglobin	Increased myoglobin
Neutrophil	Decreased neutrophil count
Platelet	Increased platelet count
	Decreased platelet count
Potassium	Increased potassium
Prolactin	Increased prolactin
Protein	Decreased protein
Prothrombin time	Increased prothrombin time
Prothrombin time	Decreased prothrombin time
Red blood cell	Decreased red blood cell count
Reticulocyte	Increased reticulocyte
	Decreased reticulocyte
Sodium	Decreased sodium
Total bilirubin	Increased total bilirubin
Triglyceride	Increased triglyceride
Triiodothyronine	Increased triiodothyronine
	Decreased triiodothyronine
Uric acid	Increased uric acid
Urine blood	Increased urine blood
Urine protein	Increased urine protein
Urobilinogen	Increased urobilinogen
White blood cell	Increased white blood cell count
	Decreased white blood cell count

abnormalities included increased prothrombin time and elevated liver functions, such as alkaline phosphatase, alanine transaminase, aspartate transaminase, and gamma-glutamyl transpeptidase levels.

The mean number of laboratory abnormalities detected for each drug was 26.9 (±7.5). The overall sensitivity, specificity, PPV, and NPV were 82.8% (±13.8%), 39.8% (±16.9%), 51.3% (±17.5%), and 76.8% (±17.1%), respectively (Table 3). In comparing the performance of the CERT algorithm for non-oncology drugs with its performance for oncology drugs, both sensitivity and specificity were similar (77.8%, 36.9% versus 94.4%, 46.5%); however, the oncology drugs evidenced a low PPV (32.1%) and high NPV (98.6%) compared with those (59.6% and 67.5%, respectively) observed with the non-oncology drugs.

Among the 269 signals detected by the CERT algorithm, 223 (83.0%) were associated with "hematopoiesis and coagulation," "hepatobiliary enzymes," and "renal function and urine tests" groups. Furthermore, CERT apparently exhibits relatively higher detection ability for the "hematopoiesis and coagulation" and "hepatobiliary enzymes" groups, as the PPV was 50.0%/87.2% and the NPV was 80.4%/72.7%, respectively. CERT detected only 19 signals associated with "lipids and metabolism" and "hormones," Therefore, the PPV values for these groups were just 23.5%/20.0%.

The average durations from the first medication to the extreme laboratory test result for true-positive signals (8.5 ± 3.5 days) and false-negative signals (12.7 ± 9.5 days) were statistically different ($p < 0.001$). The proportion of those who showed changes of laboratory test results from normal value before medication to abnormal after medication for true-positive signals and false-negative signals was 14.0% and 5.1%, respectively. These results suggest that the CERT is more suitable for acute and/or frequent ADE detection.

DISCUSSION

The results of this study demonstrate that an automated PMS system using the novel CERT algorithm to compare extreme laboratory results prior to and after medication during hospitalization can be used for almost real-time ADE signal detection, and also, that EMR data may prove to be an invaluable source of PMS data. When comparing the ADE signals detected by the CERT algorithm and the reported ADEs representing laboratory abnormalities, the sensitivity, specificity, PPV, and NPV of the algorithm for 10 drugs could be evaluated. This finding identifies the CERT algorithm as an effective method for automated ADE signal detection using an EMR database. The entire process can be automated. Even with 10 years of EMR data, only approximately 9 seconds were required to analyze the associations inherent to a "drug–laboratory abnormality" pair.

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(1) Sensitivity $= \frac{A}{A+C}$ (2) Specificity $= \frac{D}{B+D}$

	Previously known ADEs	Previously unknown ADEs
ADEs detected by CERT	A	B
ADEs not detected by CERT	C	D

(3) PPV $= \frac{A'}{A'+B'}$ (3) NPV $= \frac{D'}{C'+D'}$

	Previously known laboratory abnormalities	Previously unknown laboratory abnormalities
Laboratory abnormalities detected by CERT	A'	B'
Laboratory abnormalities not detected by CERT	C'	D'

Figure 3. The formula of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the Comparison on Extreme Laboratory Test results (CERT) algorithm. ADE, adverse drug event

Although spontaneous reporting is a representative PMS method, it requires profound efforts and costs, and suffers from significant underreporting. DA-based analytical methods suffer from the same limits as spontaneous reporting. EMR data are relatively rich in clinical content. Therefore, a clear need exists for a more complex method for the treatment of EMR data for PMS. The algorithm proposed herein, CERT, proved appropriate for automation, because of its explicit and transparent processes. Abundant data can be analyzed with the algorithm within 76 minutes for 510 unique drug–laboratory abnormality pairs, or within approximately 9 seconds for a drug–laboratory abnormality pair. Considering that the existing studies focused on just one drug–ADR pair, and that several months to years were required for each of these studies,[9,29] the analysis speed of the CERT algorithm is clearly on a different level. Such high levels of speed were also attributable, at least in part, to simple signaling rules (paired *t*-test and McNemar's test) based on naive *p*-values, high-performance computer equipment, and a well-organized data structure. Thus, the automatability and speed of the CERT algorithm and the system is expected to allow, eventually, for real-time ADR signal identification. More complex signaling rules or analogues to other data mining algorithms (e.g., Bayesian Confidence Propagation Neural Network, Multi-item Gamma-Poisson-Shrinker) may be considered in future studies, while maintaining the high speed of the current system, owing to the continuous enhancement of computing power.

With many laboratory test results of a patient during hospitalization, only a pair of pre-extreme and postextreme values was selected for analysis via the CERT algorithm. This study design is similar to a case-series method or sequence symmetry analysis in the point that we compared data from periods when patients were exposed to target drugs and data from periods when patients were not exposed. These designs have the advantage of removing confounders considered in case-control[30] or cohort studies[31]. Actually, because the first day of medication was used to divide baseline and risk period, it is closer to a case-series method than a sequence symmetry analysis, which only considers the sequence of drug administration. However, it also differs from a case-series method because we do not consider washout periods and regard whole periods after medication as risk periods. Also, it is dissimilar in that we used extreme laboratory test results, not diagnosis or symptoms.

The use of extreme, rather than mean or median values, as a representative pair may provoke controversy. However, in cases in which the mean or median values were used and a potentially causative drug was discontinued, or in cases in which an antidote to reverse ADR was administered, the transient ADR effect on laboratory results would be meaningfully mitigated, and the aforementioned abnormal laboratory results would be diluted, and ultimately disappear.

This study was limited in several ways. First, no definitive standards have yet been established for ADR identification. Published known ADEs and their

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Table 2. Epidemiologic characteristics of the study population for each drug (January 2000 to March 2010)

Drugs	Ciprofloxacin	Clopidogrel	Ketorolac	Levofloxacin	Ranitidine	Rosuvastatin	Valproic acid	Etoposide	Fluorouracil	Methotrexate
No. of cases*	16 706	19 188	82 273	9059	68 995	4811	11 523	1466	11 217	1576
No. of prescriptions	153 869	100 115	370 292	82 335	787 095	29 369	416 169	4844	60 381	3650
Age, mean (SD)	54 (16.4)	62 (12.5)	44 (17.8)	47 (17.6)	48 (21.0)	62 (12.2)	43 (23.2)	41 (22.6)	54 (11.3)	32 (20.6)
Cases with age, *n* (%)										
<5	4 (0)	8 (0)	834 (1.0)	2 (0)	2711 (3.9)	0 (0)	990 (8.6)	122 (8.3)	0 (0)	171 (10.6)
6–18	188 (1.1)	9 (0)	5172 (6.3)	209 (2.3)	4950 (7.2)	1 (0)	1409 (12.2)	213 (14.5)	8 (0.1)	375 (23.8)
19–34	1978 (11.8)	296 (1.5)	19 776 (24.0)	2258 (24.9)	8735 (12.7)	58 (1.2)	1339 (11.6)	171 (11.7)	491 (4.4)	327 (20.7)
35–49	4303 (25.8)	3030 (15.8)	26 306 (32.0)	2767 (30.5)	17 103 (24.8)	698 (14.5)	2588 (22.5)	291 (19.8)	3408 (30.4)	350 (22.2)
50–64	4732 (28.3)	6544 (34.1)	16 784 (20.4)	1913 (21.1)	16 922 (24.5)	1776 (36.9)	2696 (23.4)	419 (28.6)	4831 (43.1)	218 (13.8)
65+	5501 (32.9)	9301 (48.5)	13 401 (16.3)	1910 (21.1)	18 574 (26.9)	2278 (47.3)	2501 (21.7)	250 (28.6)	2479 (22.1)	135 (8.6)
Female, *n* (%)	7658 (45.8)	7560 (39.4)	44 715 (54.3)	4104 (45.3)	34 703 (50.3)	2067 (42.7)	4787 (41.5)	588 (40.1)	6432 (57.3)	909 (57.6)

SD, standard deviation.
*The cases were counted separately when a same patient was hospitalized again.

mapped (representative) laboratory abnormalities were used as surrogate markers for assessments of algorithm performance. However, the previously published ADE lists themselves cannot be used to confirm their identifications as true ADRs, or vice versa. ADE lists on UpToDate change constantly. For example, no renal injuries associated with clopidogrel were listed on UpToDate in March 2010; however, in the next month, the ADE of clopidogrel was listed on UpToDate. Nevertheless, the signal raised by CERT was classified as a false-positive herein, but we are not completely clear as to whether this result is a true or a false positive.

A more robust validation process could be conducted in the future, via a simulation study.

Confounding by indication must also be taken into careful consideration in future studies. Combination of CERT with an algorithm that can reduce confounding by indication might be considered.[32] Time-dependent covariate could be a confounder as well. For example, the CERT indicates that valproic acid is associated with serum creatinine increase. After close chart reviews, we found that brain injury followed by septic shock is one of the common causes for that. As these confounders can cause false or even positive signals, ADE signals detected by CERT, also signals by other quantitative methods, should be carefully considered as a supplement to qualitative investigation.

The subject populations were limited to inpatients. Multiple laboratory tests prior to and after medication were required for analysis. Thus, laboratory tests that are performed only rarely would not be included in the set of laboratory abnormalities. Drugs prescribed predominantly to outpatients were not subjected to analysis. The duration of drug exposure and drug dose were not taken into consideration herein. Only one tertiary teaching hospital's EMR database was used for evaluation. In the future, multicenter analysis will be required to generalize this algorithm.

A fully automated system using the CERT algorithm might be capable of successfully identifying previously published ADRs within a very short time by analyzing the EMR database of a Korean tertiary teaching hospital. The use of EMR databases for the detection of laboratory abnormalities after medication may prove useful in monitoring the safety of marketed drugs. If so, the technique would contribute greatly to the exploratory data analysis of the EMR database at the front-end of timely ADR-preventive strategies. EMR databases, prescription data and laboratory results in particular, would be invaluable data resources for ADR signal detection. However, despite the encouraging results of this study, the

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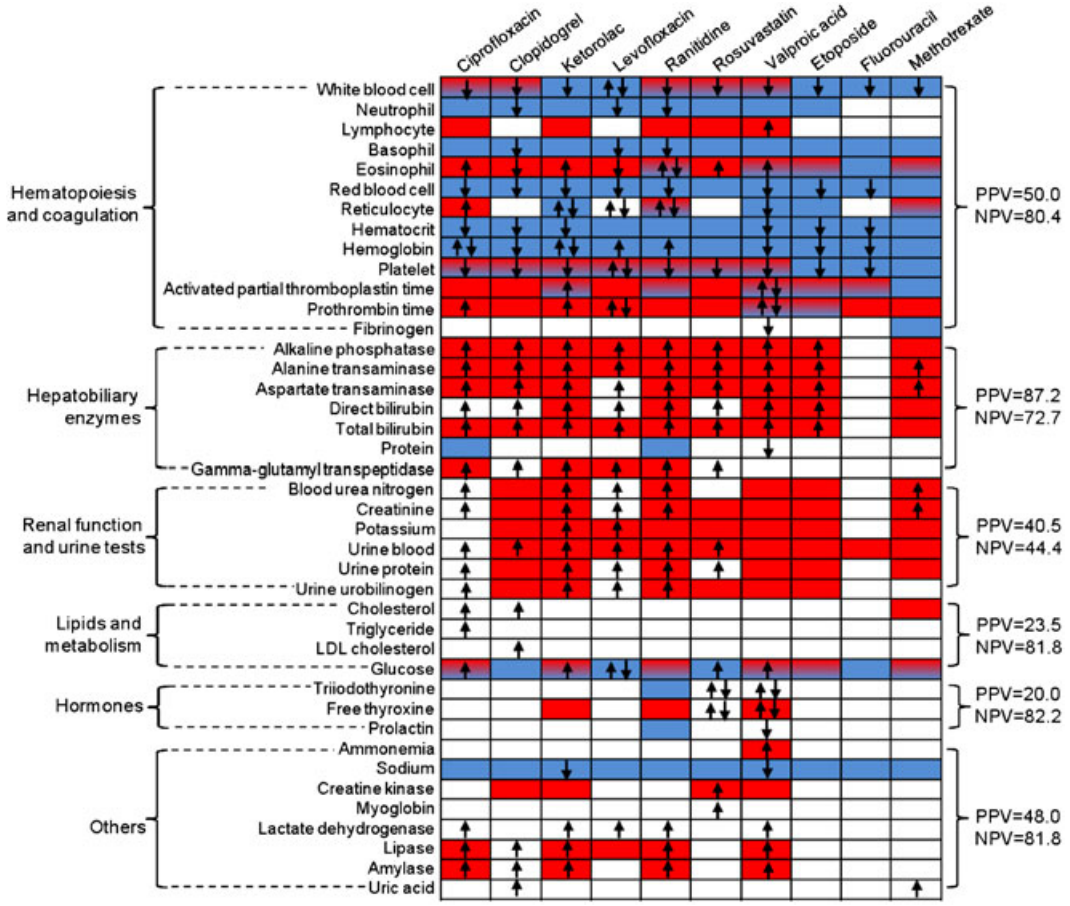

Figure 4. Previously reported laboratory abnormalities and detected laboratory abnormalities by Comparison on Extreme Laboratory Test results (CERT) algorithm. Rows represent laboratory abnormalities, and columns represent drugs. The arrows indicate laboratory abnormalities transformed from previously reported adverse drug reactions using the mapping table for each drug: "↑" and "↓" designate elevation and reduction, respectively. The colors in the cells mean signals detected by CERT. The red, blue, and red-to-blue gradient cells indicate "increase," "decrease," and "both increase and decrease" on laboratory tests after medication, respectively. PPV, positive predictive value; NPV, negative predictive value; LDL, low-density lipoprotein

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of Comparison on Extreme Laboratory Test results algorithm for each drug

	Drug	No. of detected signals*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Non-oncology drug	Ciprofloxacin	25	64.3	47.6	64.0	61.5
	Clopidogrel	25	76.9	32.6	48.0	69.2
	Ketorolac	33	95.2	37.1	75.8	83.3
	Levofloxacin	20	70.6	59.0	70.0	54.8
	Ranitidine	38	92.3	25.6	57.9	76.9
	Rosuvastatin	24	64.3	33.3	37.5	66.7
	Valproic acid	36	81.0	22.9	63.9	60.0
	Subtotal†	28.7	77.8	36.9	59.6	67.5
Oncology drug	Etoposide	28	100.0	34.6	35.7	100.0
	Fluorouracil	13	100.0	76.9	38.5	100.0
	Methotrexate	27	83.3	28.0	22.2	95.8
	Subtotal†	21.0	94.4	46.5	32.1	98.6
Total‡	Average (SD)	26.9 (7.5)	82.8 (13.8)	39.8 (16.9)	51.3 (17.5)	76.8 (17.1)

PPV, positive predictive value; NPV, negative predictive value; SD, standard deviation.
*Number of signals detected by Comparison on Extreme Laboratory Test results algorithm among 51 laboratory abnormalities.
†Average performance for non-oncology drugs and oncology drug.
‡Average performance for all 10 drugs.

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algorithm presented herein will require further evaluation for generalization.

KEY POINTS

- Quantitative analytic methods are being increasingly used in PMS.
- Currently existing methods are limited to spontaneous reporting data and are inapplicable to hospital EMR data.
- New quantitative methods are required to use EMR data as a source for ADR signal detection.
- Comparison on Extreme Laboratory Test results algorithm is a quantitative analytic method comparing extreme laboratory results prior to and after medication during hospitalization.
- The algorithm can be regarded as a useful ADR signal detection tool, which can be routinely applied to EMR data.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Supplementary Table 1. Mapping table between adverse drug events (ADEs) and laboratory test abnormalities

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