Allergy Asthma Immunol Res. 2020 May;12(3):378-380
https://doi.org/10.4168/aair.2020.12.3.378
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Active Pharmacovigilance of Drug-Induced Liver Injury Using Electronic Health Records

Sang-Heon Kim *

Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea

▸ See the article "Evaluation of Drug-Induced Liver Injury Developed During Hospitalization Using Electronic Health Record (EHR)-Based Algorithm" in volume 12 on page 430.

Received: Feb 22, 2020
Accepted: Feb 24, 2020

Correspondence to
Sang-Heon Kim, MD, PhD
Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.
Tel: +82-2-2290-8336
Fax: +82-2-2298-9183
E-mail: sangheonkim@hanyang.ac.kr

ORCID iDs
Sang-Heon Kim
https://orcid.org/0000-0001-8398-4444

Disclosure
There are no financial or other issues that might lead to conflict of interest.

Drug-induced liver injury (DILI) is relatively rare but frequently associated with serious morbidity and mortality compared to other adverse drug reactions (ADRs).[1] Severity ranges from asymptomatic mild elevation in hepatic enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) or bilirubin to liver failure and death. Thus, monitoring DILI is essential for the pharmacological treatment with hepatotoxic drugs. Furthermore, assessment of the risk of DILI in newly developed drugs is important part of pharmacovigilance. However, spontaneous reports of DILI often lead to under-report and under-estimation of the risk of DILI. While prospective observational studies could result in high-quality evidence of the risk of DILI in a specific drug in narrow conditions, a great body of resources and time is needed to draw a reasonable conclusion.

Active surveillance of ADR has been attempted to overcome the disadvantages of spontaneous reporting and post-marketing surveillance.[2] In the advent of active pharmacovigilance in various ADR, DILI has been examined for the usefulness of detection algorithms using electronic health records (EHR).[3] While the clinical course of DILI varies according to the culprit drugs or comorbidities of the subjects, the diagnosis of DILI is suspected based on the laboratory findings, including liver function tests, and exclusion of the other conditions affecting liver function abnormality. Thus, before clinical manifestations such as gastrointestinal symptoms or generalized symptoms due to liver injury or hepatic failure, surveillance of liver function tests could be used for early detection of DILI and discontinuation of the causative drugs. Unsurprisingly, laboratory data has been utilized in the detection algorithm for DILI from early days of active pharmacovigilance for DILI.[4]

In this issue of the *Allergy, Asthma & Immunology Research*, Kang and colleagues[5] have reported a multicenter observational study that investigated DILI developed during hospitalization. They enrolled 256,598 subjects who were hospitalized for 1 year in 3 tertiary university hospitals in Korea. The algorithm consisted of 2 steps using both laboratory criteria and diagnostic codes. First, the algorithm excluded subjects with no laboratory data or high level of serum ALT > 3 times upper normal limit (UNL) of or total bilirubin > 2 times UNL and included subjects with high serum ALT > 3 × UNL plus total bilirubin > 2 × UNL or ALT > 5 × UNL afterward during hospitalization. Next, they excluded subjects with diagnostic codes recorded at the time of discharge suggesting liver diseases other than DILI. Applying this

algorithm, 1,100 subjects (0.43%) were screened for suspected DILI. Further review of EHR by the specialists confirmed 365 cases of DILI. As the causative drugs for DILI, they reported antibiotics, such as piperacillin-tazobactam, and chemotherapeutic agents.

The utility of algorithms detecting DILI based on laboratory findings and/or diagnostic codes has been tested in several studies.[6-8] The novelty of these studies is that the algorithms were applied in a larger number of inpatients with higher positive predictive value than the previous studies. Use of previously developed clinical data warehouse (CDW) in the study institutions enabled the application of these algorithms. The incidence of DILI in hospitalized patients was 0.14%, which is very lower than in previous studies.[9] This might be attributed to the application of higher values of liver enzymes and bilirubin for selecting DILI. Additionally, they excluded patients with a large number of patients without laboratory data within 48 hours of admission (42.3%) and abnormally high values of liver enzymes and bilirubin (12.4%). A meta-analysis on the performance of detection algorithms for DILI showed the exclusion of specified diagnosis and designation of the drugs of interest.[3] It is well acknowledged that a diagnostic test with a high cutoff value and diagnostic criteria with strict clinical findings would lower false negative sensitivity. Thus, it would be reasonable to perform a sensitivity analysis to select the diagnostic algorithm for DILI.

The performance of the detection algorithm for DILI could be improved in the future. In addition to laboratory findings and diagnostic codes, the other signals have been tested for their usefulness in detecting DILI. For instance, searching text in EHR improved the performance of the algorithm by the elimination of text suggesting liver diseases and inclusion of text suggesting DILI.[10] Additionally, the inclusion of exposure to drugs in the algorithm also improved the diagnostic yield.[11] Incorporating the automatic causality assessment system into the algorithm can also be used for quick onsite surveillance.[12] While CDW is a useful database on active surveillance of ADR and DILI, it is limited to a single institution. Therefore, to assess the risk of DILI, a rare event of ADR, in a large population, the detection algorithm needs to be applied in multiple institutions.[13] Given the genetic susceptibility for a specific DILI, such as *N*-acetyltransferase 2 variants in antituberculosis drug-induced liver injury,[14] active surveillance of DILI could utilize both EHR and genetic databases in the future.[15]

Active pharmacovigilance based on EHR using a detection algorithm is useful in assessing of DILI in a retrospective way. A better and more sophisticated algorithm for specific drugs in specific conditions should be developed in the future. In addition, real-time onsite application of this algorithm in clinical practice would enhance early detection of DILI and decrease the morbidity and mortality of DILI.

ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0218).

REFERENCES

1. Kim SH, Naisbitt DJ. Update on advances in research on idiosyncratic drug-induced liver injury. Allergy Asthma Immunol Res 2016;8:3-11.
PUBMED | CROSSREF
2. Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, Friedman C. Novel data-mining methodologies for adverse drug event discovery and analysis. Clin Pharmacol Ther 2012;91:1010-21.
PUBMED | CROSSREF
3. Tan EH, Low EX, Dan YY, Tai BC. Systematic review and meta-analysis of algorithms used to identify drug-induced liver injury (DILI) in health record databases. Liver Int 2018;38:742-53.
PUBMED | CROSSREF
4. Pérez Gutthann S, García Rodríguez LA. The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 1993;4:496-501.
PUBMED | CROSSREF
5. Kang Y, Kim SH, Park SY, Park BY, Lee JH, An J, et al. Evaluation of drug-induced liver injury developed during hospitalization using electronic health record (EHR)-based algorithm. Allergy Asthma Immunol Res 2020;12:430-42.
6. Bui CL, Kaye JA, Castellsague J, Calingaert B, McQuay LJ, Riera-Guardia N, et al. Validation of acute liver injury cases in a population-based cohort study of oral antimicrobial users. Curr Drug Saf 2014;9:23-8.
PUBMED | CROSSREF
7. Shin J, Hunt CM, Suzuki A, Papay JI, Beach KJ, Cheetham TC. Characterizing phenotypes and outcomes of drug-associated liver injury using electronic medical record data. Pharmacoepidemiol Drug Saf 2013;22:190-8.
PUBMED | CROSSREF
8. Udo R, Maitland-van der Zee AH, Egberts TC, den Breeijen JH, Leufkens HG, van Solinge WW, et al. Validity of diagnostic codes and laboratory measurements to identify patients with idiopathic acute liver injury in a hospital database. Pharmacoepidemiol Drug Saf 2016;25 Suppl 1:21-8.
PUBMED | CROSSREF
9. Meier Y, Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier PJ, et al. Incidence of drug-induced liver injury in medical inpatients. Eur J Clin Pharmacol 2005;61:135-43.
PUBMED | CROSSREF
10. Heidemann L, Law J, Fontana RJ. A text searching tool to identify patients with idiosyncratic drug-induced liver injury. Dig Dis Sci 2017;62:615-25.
PUBMED | CROSSREF
11. Liu M, McPeek Hinz ER, Matheny ME, Denny JC, Schildcrout JS, Miller RA, et al. Comparative analysis of pharmacovigilance methods in the detection of adverse drug reactions using electronic medical records. J Am Med Inform Assoc 2013;20:420-6.
PUBMED | CROSSREF
12. Cheetham TC, Lee J, Hunt CM, Niu F, Reisinger S, Murray R, et al. An automated causality assessment algorithm to detect drug-induced liver injury in electronic medical record data. Pharmacoepidemiol Drug Saf 2014;23:601-8.
PUBMED | CROSSREF
13. Ferrajolo C, Coloma PM, Verhamme KM, Schuemie MJ, de Bie S, Gini R, et al. Signal detection of potentially drug-induced acute liver injury in children using a multi-country healthcare database network. Drug Saf 2014;37:99-108.
PUBMED | CROSSREF
14. Kim SH, Kim SH, Lee JH, Lee BH, Yoon HJ, Shin DH, et al. Superoxide dismutase gene (SOD1, SOD2, and SOD3) polymorphisms and antituberculosis drug-induced hepatitis. Allergy Asthma Immunol Res 2015;7:88-91.
PUBMED | CROSSREF
15. Choi YH, Han CY, Kim KS, Kim SG. Future directions of pharmacovigilance studies using electronic medical recording and human genetic databases. Toxicol Res 2019;35:319-30.
PUBMED | CROSSREF