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REVIEW

Risk prediction models on adverse drug reactions: A review

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Abstract

Background: The risk prediction model has become increasingly popular in recent years in helping clinical decision-making. Existing models cannot be directly applied in Indonesia. **Objective**: To review the existing prediction models and their limitations. **Method:** A search related to the prediction of ADRs risk was conducted using several journal databases: PubMed, Scopus and Google Scholar. Articles were screened to match specified criteria and further studied. **Result:** Nine articles met the criteria and were then analysed. Studies were carried out in various countries. The study population include; the elderly (>65 years, three studies), age (≥15 years, three studies), patients with Chronic Kidney Disease (CKD) (≥18 years, one study) and two studies in cancer patients. The outcomes were; ADR (five studies), ADE (two studies), DRPs (one study), and cardiovascular effects (one study). The methods for determining the predictors of ADRs all used multivariable logistic regression. **Conclusion:** Each country has different treatment patterns, prescribing practices, traditions and drug distribution, so it is necessary to develop a prediction model for ADRs that is country-specific.

Introduction

All drugs other than the expected pharmacological effects also have unwanted effects, and if these effects are harmful, the patient will experience Adverse Drug Reactions (ADRs) (Ferner and Pucci, 2020). Adverse Drug Reactions (ADRs) are among the top five causes of death in America after heart disease, stroke, cancer and lung disease (de Almeida *et al*., 2017). Minimising the occurrence of ADRs is a major challenge, which effectively requires an understanding of their frequency, severity, predictability and reversibility (Lavan and Gallagher, 2016). In recent years, risk prediction models have become increasingly popular in assisting clinical decision-making (Hendriksen *et al*., 2013). These models were developed to provide estimates of the probability of having diagnostic or developing prognostic prediction models, the latter being a particular outcome (e.g. disease, event, or complication) in an individual based on individual demographics, test results, or disease characteristics. Probability estimates can guide health workers and patients in deciding on further therapeutic management (Hendriksen *et al*., 2013). Regarding the risk prediction model for ADR events, many European countries have also developed a model, but only a few in the Asian region.

In this review article, the latest research was included with a different research population from previous

reviews. This review aimed to find out the risk prediction models that have been developed with various study populations and to identify the

limitations. This review captured recent studies related to the development of specific predictive models looking at cardiovascular effects, including studies that, in addition to model development, also compare three methods in selecting predictor factors.

Methods

Design

This study is a review of articles that correspond to the research objectives. Search articles related to ADR risk predictions using several journal databases, including PubMed, Scopus and Google Scholar. The keywords used with the help of boolean operators were *risk prediction* AND *adverse drug reactions* AND *model*. Articles related to the ADRs prediction model were analysed further. The research design for the model development is a cohort, both retrospective and prospective.

Assessment

The assessment of the selected articles was adjusted to the research objectives set by the researcher. After searching through the database, screening was carried out to find articles that matched the specified criteria. These criteria include primary research, article year from 2010 to 2022 (12 years), full text in English, conveying how to analyse data in predictor factor selection, design using a multivariable approach, and the model has been validated.

Steps used in selecting the research articles included screening, identification and eligibility following the PRISMA diagram. Articles that met the predetermined criteria were further analysed to determine the previously developed ADRs risk prediction models and their limitations. All predictor variables were determined using multivariate logistic regression.

Results

A total of nine articles met the criteria set by the author. And the articles were analysed to determine what prediction models exist and their limitations. The nine models were validated. The populations involved in the development of the models were different: three models with an elderly population (≥ 65 years), two models in patients over the age of 15 years, one model in adult patients and three models in the specific population (one adult female patient, one patient renal impairment and one chemotherapy patient). The outcomes seen at the developmental stages were also not all ADRs, but there were Adverse Drug Events (ADRs) and Drug Related Problems (DRPs).

Predictor variables from the nine studies varied. In general, the predictors of the incidence of ADRs were comorbidities, use of more than one drug, and the presence of kidney or liver disorders.

Table I: Risk prediction model development

Authors	Study setting	Study population	Methods in the development stage	Outcome	Predictor selection method
Onder *et al.*, 2010	University-based hospital Italy	Elderly (≥65 years of age)	Retrospective cohort	ADRs	Multivariate Logistic regression
O'Connor *et al.*, 2012	Teaching Hospital Ireland	Elderly (≥65 years of age)	Prospective cohort	ADRs	Multivariate Logistic regression
Sakuma *et al.*, 2012	University Hospital Japan	≥ 15 years old	Prospective cohort	ADEs	Multivariate Logistic regression
Tangiisuran *et al.*, 2014	Teaching Hospital United Kingdom	Elderly (≥65 years of age)	Prospective cohort	ADRs	Multivariate Logistic regression
Sharif-Askari *et al.*, 2014	Renal Unit Hospital Dubai: United Arab Emirates	Renal failure patients (≥18 years old)	Prospective cohort	ADRs	Multivariate Logistic regression
Urbina *et al.*, 2014	University Hospital Barcelona, Spain	≥ 15 years old	Prospective observation	DRPs	Multivariate Logistic regression
Winterstein *et al.*, 2017	University of Florida Hospital	Adult patients	Retrospective study	pADE	Multivariate Logistic regression
Kim *et al.*, 2021	Medical Centre Korea	Adult female patients	Retrospective study	Cardiovascular effects	Multivariate Logistic regression
On J *et al.*, 2022	Tertiary Teaching Hospital Korea	Adult patients	Retrospective study	Chemotherapy -induced ADRs	Logistic regression, a decision tree, an artificial neural network

Table II: Predictor variable, risk prediction model validation and limitation

Author, years	Risk prediction variable	OR (95% CI)	Validation methods	Limitation
Onder *et al.*, 2010	≥ Four comorbid condition	1.31 (1.04 – 1.64)	Cohort	Specific in elderly and European settings, cannot be extrapolated to other countries
	Heart failure	1.79 (1.39 – 2.30)		
	Liver disease	1.36 (1.06 – 1.74)		
	≥Eight drugs	4.07 (2.93 – 5.65)		
	Previous ADR	2.41 (1.79 – 3.23)		
	Renal failure	1.21 (0.96 – 1.51)		
O'Connor *et al.*, 2012	Age ≥85 years	2.22 (1.68 – 4.23)	Cohort	Specifically in the elderly and Ireland setting
	Renal failure	1.81 (1.12 – 2.92)		
	Liver disease	1.86 (0.09 – 3.84)		
	Number of STOPP medication	2.40 (1.26 – 4.59)		
	Increasing number of medication	1.09 (1.02 - 1.17)		
	Inappropriate			
Sakuma *et al.*, 2012	Doctor in charge (resident)	1.3 (1.0 – 1.7)	Cohort	Specific in the study setting
	Scheduled operation	1.2 (0.9 – 1.6)		
	Dyspnea (present)	1.5 (1.1 – 1.9)		
	Consciousness	1.6 (1.1 – 2.6)		
	The burden of illness (Charlson comorbidity index)	2.3 (1.7 – 3.3)		
	Dementia	2 (1.3 – 3.0)		
	Hemiplegia	1.5 (1.4 – 2.5)		
	Cancer			
	Medication prescribed before admission (laxatives)			
Tangiisuran *et al.*, 2014	Hyperlipidemia	3.32 (1.81 – 6.07)	Cohort	Specific in elderly and European settings
	Number of medications (≥8)	3.30 (1.93 – 5.65)		
	Length of stay ≥12 days	2.67 (1.35 – 3.49)		
	Use of antidiabetic agent	1.91 (1.04 – 3.49)		
	High WBC count on admission	1.55 (0.94 – 2.55)		
Sharif-Askari *et al.*, 2014	Age ≥65 years	1.16 (0.62 – 2.17)	Cohort	Risk score developed based on CKD hospitalised patients
	Female sex	1.33 (0.73 – 2.41)		
	ESRD, Conservative management	2.39 (1.21 – 47.4)		
	Vascular disease,	2.36 (1.24 – 4.46)		
	Serum albumin <3,5 g/dl,	2.24 (1.21 – 4.14)		
	>10 mg/L serum C-reactive protein	2.41 (1.33 – 4.37)		
	≥8 number of medication	4.64 (2.51 – 8.59)		
Urbina *et al.*, 2014	Age > 60 years	1.20 (1.01 – 1.36)	Cohort	Limited in age >60 years old Reproducibility of the developed model
	Charlson index = 2	1.33 (1.18 – 1.50)		
	Number of drugs during admission >10	3.34 (2.96 – 3.76)		
Winterstein *et al.*, 2017	Number of medication	NA	Bootstrapping	Reproducibility is limited to study data
	Length of stay			
Kim *et al.*, 2021	No. of cardiovascular risk factors*	HR: 1.91 (1.16 – 3.13)	Cohort	Specific study population among female patients
	No. of prior cardiovascular diseases	HR:4.24 (1.29 – 13.91)		
	Doxorubicin equivalent dose per 100mg/m^2	HR:1.97 (1.23 – 3.13)		
	Left-sided radiation therapy	HR:2.73 (0.71 – 10.58)		
	Endocrine therapy	HR:1.2 (0.13 – 1.66)		
	Trastuzumab	HR:2.27 (0.59 – 18.68)		
On J *et al.*, 2022	Female sex	NA	Cohort	Specific in cancer patients
	Previous history of ADRs			
	Comorbidity			

Note: WBC (white blood cell); GFR (glomerulus filtration rate); ESRD (end-stage renal disease); CHF (congestive heart failure); TIA (transient ischemic attack), NA= (not available)

Discussion

The risk prediction model can be used to estimate the possibility of having a diagnostic model or the development of a particular disease or outcome (prognostic model). In clinical practice, this model provides information to patients and guides therapy management (Hendriksen *et al*., 2013).

The risk prediction model estimates the risk (absolute probability) of the presence or absence of an outcome or disease in an individual based on the individual's clinical and non-clinical characteristics. Depending on the amount of time until outcome assessment is done, predictive research can either be diagnostic (outcome or current disease) or prognostic (outcome occurs over a while) (Hendriksen *et al*., 2013).

In developing a risk prediction model, it is important to consider whether a new model is needed. The literature should be reviewed to identify, evaluate, and consider the potential for updating existing models. Once a new risk prediction model is deemed necessary, its development is a balancing act between clinical usefulness, statistical performance, and functionality (Grant *et al*., 2018).

Prognostic studies are inherently longitudinal, most often performed in groups of patients (cohorts), which are followed over time for outcomes (or "*events*" or " *endpoints*") to occur. Cohorts are defined by the presence of one or more specific characteristics, such as having a certain disease, living in a certain place, having a certain age, or being born alive. Several types of cohort studies can be used for prognostic modelling. The most commonly used type is the single-centre retrospective cohort study.

Most of the existing risk prediction models in the development stage involve the elderly population. Model development is more in the European region; in Asia only a few have been found. The development of predictive models of ADRs in each country is different due to the practice of administering drugs to different patients, different cultures, beliefs and different diets. Therefore, the existing models are sometimes not suitable to be applied in other regions or countries. This is the limitation of each developed model. Existing models are specific to the study population and to the region or country where the model was developed. For example, The GerotoNet ADR risk score is a practical, efficient and easy method to identify patients who are at high risk of experiencing ADRs. Research by O'Connor (O'Connor *et al*., 2012) is a revalidation of The GerotoNet ADR risk Score, in his study, there is an additional predictor variable, namely; "*inappropriate medication*" which has not previously been identified in The GerotoNet Risk Score. Risk prediction models developed and included in this review are considered effective in identifying patients who are at risk but can only be applied to certain populations and cannot be extrapolated to other countries.

The limitations of this study are that the determination of the articles included in the review was adjusted to the objectives, and a critical appraisal has not been carried out for each article included in the review.

Conclusion

Based on the literature search, research related to the development of ADR risk prediction models is mostly in European countries and limited study in the Asian region. The prediction model developed has limitations that can only be applied to certain populations according to the population when the model was developed. Models that have been developed and validated cannot be extrapolated to other countries or different patient populations from the initial population the model was developed. Each country has different treatment patterns, prescribing practices, traditions and drug distribution, so it is necessary to develop a prediction model for ADRs appropriate in specific countries.

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