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BRIEF REPORT

Preliminary prediction model for identifying patients with the possibility of pharmacotherapy improvement

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KEYWORDS
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Abstract
Objective: To develop a prediction model for identifying patients with the possibility of improving pharmacotherapy during the process of pharmaceutical validation of the prescription.
Method: Cross-sectional study over two months, performed in the Internal Medicine and Infectious Disease divisions. Detecting opportunities for improving quality of pharmacotherapy is done by means of a pharmacist's validation of the prescription. Based on the information we obtained through this process, we performed a multivariate logistic regression analysis using as prognostic factors the demographic, pharmacotherapy and clinical variables related to identifying any drug-related problems (DRPs) in the patient. The model's prediction validity was assessed using the diagnostic performance curve and calculating the area under it.
Results: The final prediction model included the variables age, cardiovascular drugs (digoxin) and drugs for which a dosage adjustment is recommended in the case of organ failures. Analysis of the ROC curve showed an estimated area under the curve AUCROC) of 84.0%(95%CI: 80.5-87.1), a sensitivity value of 28% (95% CI: 24.07-32.19), a specificity value of 99.10% (95% CI: 97.80-99.73), a positive predictive value of 77.78%and a negative predictive value of 92.41%
Conclusion: The resulting prediction model enables population-based detection of pharmacotherapy safety risks in adult patients admitted to the selected hospital units. The predictive variables used by the model are commonly used in daily practice.

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PALABRAS CLAVE
Calidad;
Seguridad;
Validación farmacéutica de la prescripción;
Modelo predictivo

Modelo predictivo preliminar para la identificación de pacientes con oportunidades de mejora farmacoterapéutica

Resumen
Objetivo: Desarrollar un modelo predictivo para la identificación de pacientes con oportunidades de mejora en la farmacoterapia durante el proceso de validación farmacéutica de la prescripción.
Método: Estudio transversal de dos meses de duración realizado en los servicios de medicina interna y enfermedades infecciosas. La detección de oportunidades de mejora en la calidad de la farmacoterapia se efectuó mediante validación farmacéutica de la prescripción. A partir de la información obtenida en este proceso se realizó un análisis mediante regresión logística multivariante utilizando como factores pronóstico variables demográficas, farmacoterapéuticas y clínicas relacionadas con la identificación en el paciente de problemas relacionados con la medicación. La validez predictiva del modelo se evaluó mediante la curva de rendimiento diagnóstico y el cálculo de su área.
Resultados: El modelo predictivo final incluyó las variables edad, fármacos cardiovasculares (digoxina) y fármacos en los que se recomienda el ajuste posológico por insuficiencias orgánicas. El análisis de la curva ROC mostró un área bajo la curva estimada del 84,0% (IC 95%: 80,5-87,1), un valor de sensibilidad del 28% (IC 95%: 24,07-32,19), un valor de especificidad del 99,10% (IC 95% 97,80-99,73), un valor predictivo para positivos del 77,78%y un valor predictivo para negativos del 92,41%
Conclusión: El modelo predictivo obtenido permite la detección poblacional del riesgo de seguridad farmacoterapéutica en los pacientes adultos ingresados en los servicios hospitalarios seleccionados. Las variables predictoras manejadas por el modelo son habitualmente utilizadas en la práctica asistencial diaria.

Introduction

The principle objective of pharmacotherapy quality control programs is to guarantee that there is no risk attached to the pharmaceutical for the patient. The prescription is the process in the therapeutic chain most strongly implicated in medication errors (ME),[1,2] with an incidence of 0.4%11%; of these, 1% reach the patient and produce real pharmacotherapeutic morbidity (PTM).[2-4] Consequently, quality criteria or pharmacotherapeutic alerts need to be established beforehand to be able to identify a patient with preventable PTM (as a consequence of ME).[5] These criteria or alerts would detect any occurrence that may potentially harm the patient. The pharmaceutical validation process of prescriptions constitutes a key process (adds value) before they are dispensed that attempts to prevent, identify, and resolve these drug-related problems (DRP).[6] In this context, a more effective prescription system must be developed and possible risk factors should be established.[7-11].

The objective of this study is to develop a predictive model to detect adult hospitalised patients whose pharmacotherapy can be improved during the pharmaceutical validation process of prescriptions.

Materials and methods

The study population was made up of randomly selected adult patients admitted to a hospital with a hand-written prescription system. The patients were admitted to the departments of internal medicine and infectious diseases unit (IDU). We included all patients with at least one pharmacotherapeutic prescription during the hospitalisation period.

A two-month cross-sectional study was performed in which we analysed all pharmacotherapeutic prescriptions. We identified opportunities to improve the pharmacotherapy by validating the prescription by various different pharmacists. The pharmacotherapeutic medical history, laboratory data, pharmacokinetics, and communication with the rest of the multidisciplinary team were used as sources of support, as well as the current prescription validation guidelines at the study hospital.[12-14] A model with standardised documentation was used to classify and analyse the ME/DRP.[6]

We performed a multivariate logistic regression statistical analysis in which the dependent variable was the presence of DRP in the prescription. The predictive variables studied were the following: age (years), sex, presence of allergies, serum creatinine (mg/dl), bilirubin greater than or equal to 2 mg/dl, number of comorbidities greater than or equal to 2, creatinine clearance at or below 50 ml/min, prescription of drugs associated with a greater risk of adverse effects (opiates, antibiotics [vancomycin, gentamycin, and imipenem], digoxin, and anticoagulants) in the literature,[9] intravenously administered drugs, drugs requiring dosage adjustments, unstandardised intravenous mixtures with risk of physicochemical instability,[13] and number of medications.

We calculated the sample size assuming an incidence of DRP associated with the prescription of 10%, and a maximum of 4-5 variables in the final model.[15] The predictive model was carried out according too Hosmer and Lemeshow (2000).[16] Potential predictive factors were selected by applying univariate logistic regressions ($P \leq .3$).[17] We

investigated the multivariate models obtained using criteria for inclusion and exclusion of variables with a value of 0.05 and 0.1, respectively. Interaction terms were entered in the models in order to see if the adjustment indices improved ($P<.05$). We performed all statistical analyses using SPSS software, version 15 (SPSS Inc, Chicago, IL). The final model was chosen based on the area under the ROC curve and the theoretical and practical advantages and disadvantages. The validity indices for the selected model were calculated. Lastly, we evaluated the discrimination of the final chosen model for both clinical departments studied.

Results

A total number of 65 patients were included in the study, which constituted 2.7% of those admitted/year who were treated at the study hospital. A total of 492 prescriptions were analysed, with a mean of 9.82 prescriptions per patient (95% CI: 8.19-11.44). Table displays the descriptive characteristics of the variables analysed.

A total of 24 patients were identified with DRP (36.9%), and 53 prescriptions had DRP (10.8%). The profile of the DRP identified, according to category, was the following: DRP of effectiveness (15.1%), and of safety (84.9%); of this second category, overdosing was most common (93.3%), with adverse reactions composing the rest of the cases (6.7%). The drugs implicated in these DRP were the following: anticoagulants (22.6%), opioid analgesics (1.9%), antibiotics (41.4%) (vancomycin [7.5%], gentamicin [1.9%], and imipenem [7.5%]), digoxin (18.9%), and others (15.1%).

The univariate analysis excluded plasma creatinine ($P=.837$), total bilirubin greater than or equal to 2 mg/dl ($P=.998$), and the prescription of opioid drugs ($P=.706$) from the model. After evaluating first order interactions, these were excluded as they were not significant. The mathematical expression of the final model is explained in Figure 1. The area under the ROC curve was 84.0% (95% CI: 80.5-87.1), and the optimal cut-off point for DRP probability was 0.543 (Figure 2). For this cut-off point, the test has a sensitivity of 28% (95% CI: 24.07-32.19), a specificity of 99.10% (95% CI: 97.80-99.73), a positive predictive value of 77.78%, and a negative predictive value of 92.41%. The analysis of the profile of predictions by clinical department obtained null results for sensitivity and positive predictive value for patients in the IDU.

Discussion

One proposal for the early identification of opportunities for improvement before DRP reach the patient is the risk

Table 1 Descriptive characteristics of the variables

	Internal medicine	IDU	Total
	Mean (SD) or No. (%)	*Mean (SD) or No. (%)*	*Mean (SD) or No. (%)*
No. of patients	37 (56.9)	28 (43.1)	65 (100)
Age, years	76.9 (12.3)	55.4 (22.8)	67.9 (20.3)
Female	17 (45.9)	13 (46.4)	30 (46.2)
Creatinine, mg/dl	1.6 (0.9)	0.8 (0.6)*	1.0 (1.1)*
Creatinine clearance ≤50 ml/min	18 (48.6)	6 (21.4)	24 (36.9)
Total bilirubin, mg/dl	0.69 (0.34)	0.50 (0.40)*	0.63 (0.34)*
Total bilirubin ≥2 mg/dl	0 (0)	3 (10.7)	3 (4.6)
Allergy	10 (27)	4 (14.3)	14 (21.5)
No. of comorbidities ≥2	14 (37.8)	10 (35.7)	24 (36.9)
Total number of prescriptions	287 (58.3)	205 (41.7)	492 (100)
Mean number of prescriptions/patient	9.7 (6.1)*	10.0 (7.2)*	9.8 (6.6)*
Mean number of medications/prescription	3.44 (3.27)	3.74 (3.42)	3.56 (3.33)
Prescriptions with drugs associated with ADE	54 (18.8)	25 (12.2)	79 (16.1)
Cardiovascular (digoxin)	18 (6.3)	6 (2.9)	24 (4.9)
Antibiotics (vancomycin, gentamicin, imipenem)	15 (5.2)	17 (8.3)	32 (6.5)
Anticoagulants	15 (5.2)	11 (5.4)	26 (5.3)
Opioids	14 (4.9)	0 (0)	14 (2.8)
Prescriptions with drugs that require adjustment due to organ failure	82 (28.6)	51 (24.9)	133 (27.0)
Prescriptions with intravenous drugs	167 (58.2)	101 (49.3)	268 (54.5)
Prescriptions with unstandardised intravenous mixtures at risk of physicochemical instability	42 (14.6)	17 (8.3)	59 (12.0)
Total number of prescriptions with DRP	45 (84.9)	8 (15.1)	53 (100)

ADE indicates adverse drug events; DRP, drug-related problem; IDU, infectious disease unit; SD, standard deviation.
*Non-normal distribution: median (IQR).

$$Pr\,(Y=1/X) = \frac{1}{1+e^{-(5.965+0.030XAge\ (years)+1.384XDigoxin+2.635XDosage\ adjustment)}}$$

Figure 1 Mathematical expression of the predictive model.

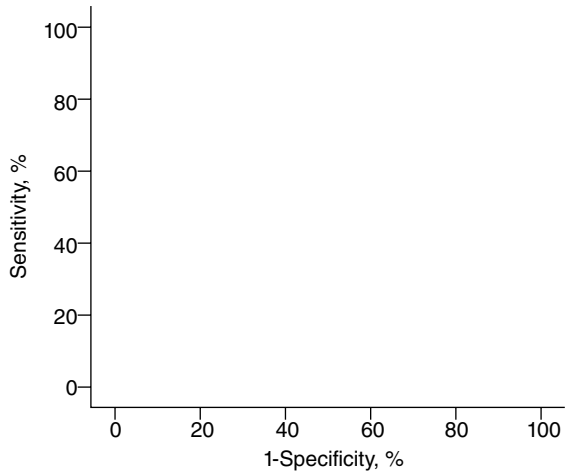

Figure 2 Diagnostic performance curve.

stratification based on a group of prospectively evaluated parameters.[18] Similarly, this study has proposed a predictive model for the detection of patients at risk of DRP during the pharmaceutical validation process of prescriptions. This allows these prescriptions to be classified into high or low risk categories.

The incidence of DRP detected in all prescriptions analysed was 10.8%, which is similar to the value of 11% presented by other authors.[2] We observed in the analysis of the type of DRP that the principal cause was dosage ME (88.7%), with the tendency towards over-dosage (79.2%). This result was similar to those found by Dean et al.[4] The profile of drugs implicated in DRP also resulted in data that coincided with other publications.[9] This showed that antibiotic drugs, cardiovascular agents, and anticoagulants are those most likely to cause DRP.

The variable with the greatest potential for risk of DRP in our model was the prescription of drugs that require dosage adjustments due to organ failure (OR=2.635). The most common dosage adjustment is due to kidney failure, which is detected in several different drug programs at incidences of 10% 23.2% in validated pharmacotherapeutic prescriptions.[19,20] The fact that the variable of creatinine clearance below or equal to 50 ml/min was not incorporated in our final model could be due to its binary categorisation.

The final predictive model enabled patients with a high risk of DRP to be detected with a high specificity (99.10%), although the sensitivity did not surpass 28%. This result appears to point to the use of loose criteria that are not sensitive to the presence of DRP, and which would improve with a complete evaluation of the patient focussing on clinical aspects that are more closely related to the presence of PTM. To this end, a decentralised pharmaceutical care that is close to the patient is required, which has been shown to increase the overall rate of DRP identified.[21] However, the specificity and predictive values obtained make this a useful tool when having to correctly rule out patients with a low-risk of DRP in their prescriptions.

The limitations of this study are: the variability in the application of the different validation criteria of the prescriptions, which makes it difficult to generalise the results; and the small predictive value of the model in subpopulations of patients, such as those in the IDU. These limitations make it necessary to validate the model using a concordance analysis of the different pharmaceutical validation criteria and to widen the study population to other hospital departments.

In conclusion, the predictive model we have developed could be a useful tool for the detection of patients with the opportunity for improving their pharmacotherapy within the hospital using a few predictive variables that are easily accessible in daily clinical practice.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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