Design and validation of a predictive model for 1-year hospital admission in HIV patients on antiretroviral treatment

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ABSTRACT

Objectives To develop and validate a model for predicting the risk of hospital admission within 1 year in the HIV population under antiretroviral treatment.

Methods We conducted a retrospective observational study. Patients receiving antiretroviral treatment for at least 1 year who were followed by the pharmacy service in a Spanish-speaking hospital between January 2008 and December 2012 were included. Demographics, and clinical and pharmacotherapy variables, were included in the model design. To find prognostic factors for hospital admission a multivariate logistic regression model was created after performing a univariate analysis. Model validity was determined by the shrinkage method and the model discrimination by Harrell's C-index.

Results 442 patients were included in the study. The variables 'CD4 count <200 (cells/μL)', 'drug/alcohol use', 'detectable viral load (>50 copies/mL)', 'number of previous admissions', and 'number of drugs different from antiretroviral treatment' were the independent predictors of risk of hospital admission. Probabilities predicted by the model showed an R^2=0.98 for the development sample and an R^2=0.86 for the validation sample. The Harrell's C index for the development and validation data were 0.82 (95% CI 0.77 to 0.87) and 0.80 (95% CI 0.73 to 0.88), respectively.

Conclusions The model developed in this study may be useful in daily practice for identifying HIV patients at high risk of 1-year hospital admission.

INTRODUCTION

The morbidity and mortality rates associated with HIV have been drastically reduced since the introduction of highly active antiretroviral treatment (HAART) in 1996.

Currently, HIV has become a chronic disease[1] and, as a result, HIV-infected individuals are becoming older.[2] It is projected that by 2015, more than half of all HIV-infected individuals in the USA will be ≥50 years of age.[3]

Compared with age-matched HIV-uninfected individuals and with younger HIV-infected individuals, HIV-infected people ≥50 years have a higher rate of co-morbidities and polypharmacy, possibly exacerbated by HIV infection or long-term exposure to HAART.[4] The consequences of polypharmacy may include drug–drug interactions, toxicity, treatment failure or development of viral resistance to HAART. In addition, complex medication regimens are associated with poor adherence which can lead to an increase in hospital admissions.[5 6]

An ageing HIV population demands a new approach to the management of HIV infection. Risk prediction algorithms appear to be a good way to stratify and subsequently identify patients who need further evaluation in a multidisciplinary approach.

There are currently several methods to predict unplanned hospital admissions in patients with chronic diseases.[7 8] Due to the unique characteristics of the HIV population, models to predict 30-day risk of readmission among this population have been developed.[9 10] However, 30 days is not always long enough to perform medical interventions in order to prevent a hospital admission.

Therefore, the main objective of this study was to develop and validate an accurate tool for predicting risk of hospital admission within 1 year in the HIV population that is under HAART.

METHODS

We conducted a retrospective observational study. Patients under HAART for at least 1 year who were followed by the pharmacy service in a Spanish-speaking hospital between January 2008 and December 2012 were included. We excluded patients enrolled in clinical trials and patients whose data were not available.

The occurrence of hospital admission in HIV patients under HAART was considered the dependent variable. We considered a hospital admission when the length of stay in the hospital was >24 h. We excluded emergency department visits.

We also collected the following independent variables: demographics, laboratory values, clinical parameters, pharmacotherapy related features, and variables related to hospital admission. The co-morbidities were classified according to the definition of Rivas Costa *et al*[11] and Ollero *et al*.[12] Adherence to HAART was assessed using electronic pharmacy refill records. The threshold for optimal adherence was defined at 90% and above.

The data were collected 1 year before the first hospital admission during the study period. In those patients who were not hospitalised during the study period, variables were collected 1 year before the last visit to the pharmaceutical care office. The data were obtained through outpatient electronic medical records, by reviewing the medical history of each patient, and through the patient census report from the hospital.

Statistical analysis

Quantitative variables are expressed as mean and SD. In the case of a skewed distribution variables

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are expressed as median and percentile P25 and 75, the difference between being the IQR. Qualitative variables are expressed as absolute numbers (n) and percentages (%).

To identify independent predictors of hospital admission, univariate logistic regression was performed. Afterwards, those variables that showed statistical significance in the univariate analysis and those with a value of p≤0.25 were included in a multivariate logistic regression.

Shrinkage method was used to evaluate the validity of the prediction model. Model discrimination was determined by calculating the Harrell's C index. It was performed on both the original and the adjusted model. To verify the validity of the model the difference between both Harrell's C indexes had to be <0.10.

Calibration was tested by the Hosmer-Lemeshow 'goodness-of-fit' test and the slope of the calibration curve.

Data analysis was carried out using the statistical package SPSS V.20.0 for Windows.

Ethical issues

The study design was approved by the local ethics committees of the participating study site (0009/13).

RESULTS

Four hundred and forty-two patients were included in the study. Demographics and clinical characteristics are provided in table 1.

Most of the patients were men and the median age was 45 years. Regarding clinical characteristics, there was a high prevalence of HIV/hepatitis C virus (HCV) co-infected patients (69.5%). In addition, most of the patients were considered to adhere to their treatment (67.4%). Consequently, the majority of patients had an undetectable viral load (74.4%) and a CD4 count >200 cells/μL (81.2%). Considering the antiretroviral drug classes, the most common regimens were those including a combination of a nucleoside reverse transcriptase inhibitors and a protease inhibitor. In addition to HAART, the median number of co-medications was 2.

Variables that reached statistical significance in the univariate regression analysis were: demographics, adherence ≥90%, CD4 count <200 cells/μL, drug/alcohol use, detectable viral load (>50 copies/mL), AIDS, HIV transmission mode, number of co-morbidities, number of previous admissions, number of drugs different from HAART, HAART including integrase inhibitors, CCR5 receptor antagonists or non-nucleoside reverse transcriptase inhibitors. Table 2 shows the relationship between these variables and the risk of hospital admission.

Subsequently, multivariate analysis showed that a CD4 count <200 cells/μL, drug/alcohol use, detectable viral load (>50 copies/mL), number of previous admissions, and number of drugs different from HAART were the only independent predictors of risk of hospital admission (table 3).

The mathematical model for predicting risk of hospital admission within 1 year in the HIV population is shown in box 1.

In figure 1, receiver operating characteristic (ROC) curves of logistic regression for both development and validation data are plotted.

The Harrell's C index for the development and validation data were 0.82 (95% CI 0.77 to 0.87) and 0.80 (95% CI 0.73 to 0.88), respectively. They both have values of Harrell's C >0.75, showing good discriminatory ability. The difference between both Harrell's C statistics was <0.10 (0.82 to 0.80=0.02) so discriminant validity is supported.

The calibration curves for development and validation data are shown in online supplementary figures 1 and 2. The slope values were R^2=0.98 and R2=0.86, respectively.

Internal consistency reliability as measured by Cronbach's α was 0.99 and 0.96 in the development and validation samples, respectively.

Finally, model calibration is graphically shown by risk deciles in online supplementary figures 3 and 4.

Table 1 Baseline and clinical characteristics of the patients included in the study

Variable	Characteristics
Age in years, median (IQR)	45.00 (41–48)
Sex: male/female (% male)	357/85 (80.8%)
Serum bilirubin (mg/dL), median (IQR)	0.53 (0.37–0.84)
Serum creatinine (mg/dL), median (IQR)	0.78 (0.69–0.91)
CD4 count <200 cells/μL, n (%)	82 (18.6%)
Detectable HIV viral load (copies/mL), n (%)	113 (25.6%)
HIV transmission mode, n (%)	
Injection drug use	322 (72.9%)
Sexual	120 (27.1%)
HIV/HCV co-infection, n (%)	307 (69.5%)
Alcohol or drug use, n (%)	158 (35.7%)
Co-morbidities, median (IQR)	2.00 (1.00–3.00)
AIDS, n (%)	297 (67.2%)
Type of HAART, n (%)	
2 NRTI+1 NNRTI	200 (45.2%)
2 NRTI+1 PI	238 (53.8%)
Others (including CCR5 antagonists or IntIn)	44 (10.0%)
Adherence to HAART ≥90%, n (%)	298 (67.4%)
Co-medications, median (IQR)	2.00 (0.00–4.00)
Days of hospital stay, median (IQR)	8.00 (5.00–12.75)
Hospital admissions the year before, minimum–maximum	0–7

HAART, highly active antiretroviral treatment; IntIn, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitors.

DISCUSSION

Our study is the first to present a mathematical model for predicting risk of hospital admission within 1 year in an HIV population under HAART. The risk factors identified are associated with the following variables: CD4 count <200 cells/μL, detectable HIV-RNA level (>50 copies/mL), drug/alcohol use, the number of co-medications for diseases that are not HIV, and finally the number of previous admissions.

To date several risk prediction models for hospital readmission in the general population have been published. The following predictor variables were identified by some studies:

Table 2 Univariate analysis*

Variable	HR (95% CI)
Adherence to HAART ≥90%	0.28 (0.17 to 0.47)
CD4 count <200 cells/μL	7.35 (3.45 to 15.62)
Alcohol or drug use	5.91 (3.51 to 9.96)
Detectable HIV viral load (copies/mL)	4.26 (2.41 to 7.54)
AIDS	2.63 (1.59 to 4.36)
HIV transmission mode	0.40 (0.24 to 0.68)
Number of co-morbilities	1.33 (1.11 to 1.60)
Hospital admissions the year before	14.70 (4.49 to 48.10)
Number of co-medications	1.42 (1.26 to 1.60)

*Only variables with a significant association with risk admission are included.

Table 3 Multivariate analysis*

Variable	HR (95% CI)
CD4 count <200 cells/μL	3.18 (1.33 to 7.61)
Alcohol or drug use	4.13 (2.30 to 7.39)
Detectable HIV viral load (copies/mL)	2.11 (1.05 to 4.23)
Hospital admissions the year before	6.57 (1.85 to 23.36)
Number of co-medications	1.25 (1.10 to 1.42)

*Only variables with a significant association with risk admission are included.

demographics, type of diagnosis, and number of previous admissions.[13 14] Others studies have included independent variables such as laboratory values, number of prescription drugs or socioeconomic status. Prediction models based only on one variable, such as the number of previous admissions, have little validity because they do not provide enough clinical information.[15–17]

In our study the type of HAART has not been shown to predict hospital admission within 1 year. Different conclusions can be drawn from other papers.[6] The use of different types of HAART is probably the main cause of the differences between both studies. It is known that significant advances in antiretroviral therapy have been made recently and as a result antiretroviral agents are safer and simpler than before.

Fielden *et al*[18] and Juday *et al*[19] have found that adherence is a key factor in decreasing the risk of hospitalisation. In this study poor adherence to antiretroviral treatment was not an independent predictor. However, undetectable viral load was an independent variable of hospitalisation. Although it has been widely demonstrated that incorrect adherence is one of the main causes of treatment failure, it is possible that other variables such as co-infection or HIV drug resistance are associated with treatment failure.

Our study shows the number of co-medications for other chronic diseases (non-HIV drugs) predicts the risk of hospital admission. Cantudo-Cuenca *et al*[20] reported that the use of multiple medications increases the risk of non-adherence and therefore it may increase the risk of hospital admission. Polypharmacy seems to be the next therapeutic challenge in HIV patients.[21–23]

Co-morbidities were related to the risk of admission only in the univariate analysis. According to Crowell *et al*,[24] HCV and/or hepatitis B virus (HBV) co-infected patients have higher rates of admissions than HIV mono-infected patients. Despite the high rates of co-infected patients in our study, we did not find this association, possibly because we did not measure the degree of liver damage.

The number of previous hospitalisations was a predictor of readmission. Most readmissions occur within a week of discharge. Pharmaceutical interventions within the first few days would help prevent readmissions.

There is also a role for pharmacists in decreasing the errors in prescribing antiretroviral drugs during the hospitalisation. These errors can lengthen their hospital stay so a close monitoring of these patients should be a priority.[25 26]

Box 1 Mathematical model for predicting risk of hospital admission within 1 year in HIV population

Prob (risk of hospital admission within 1 year in HIV population under HAART)=$1/(1+e^{-Z})$

Z=−14 857+1744×hospital admissions the year before +02 663×number of co-medications+0771×detectable HIV viral load (copies/mL)+13 584×alcohol or drug use+11 376×CD4 count (<200 cells/μL).

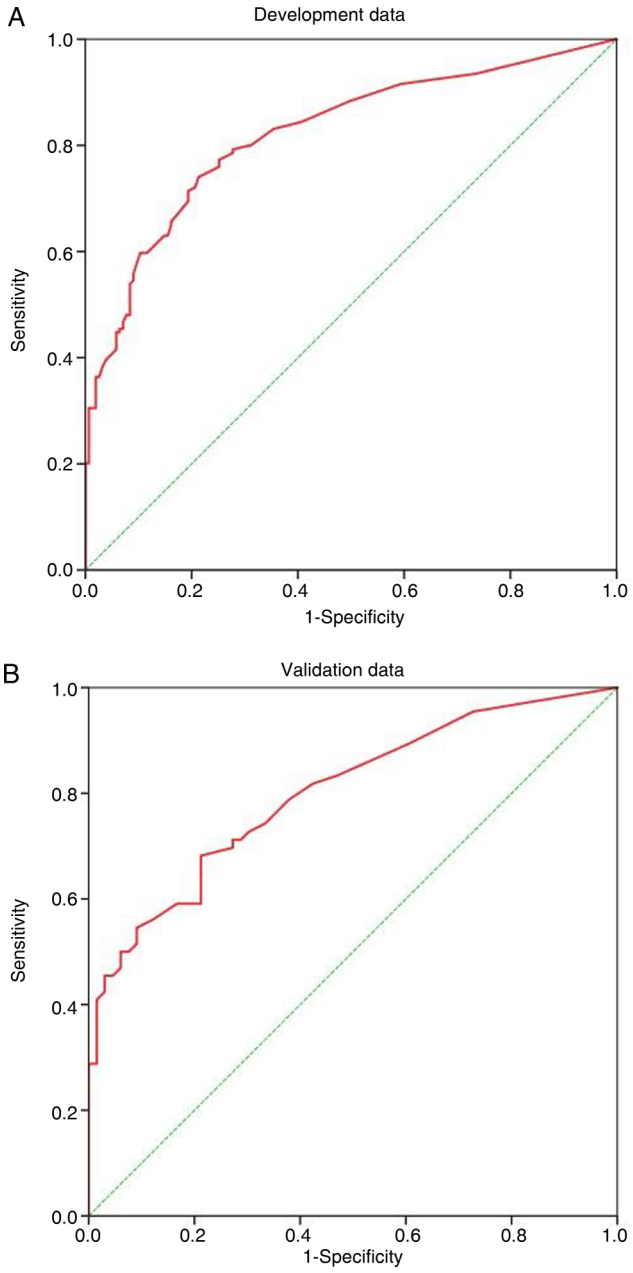

Figure 1A, B Curves of logistic regression for development and validation data.

Limitations

The main limitation of this study is its design. Failure to include patients from different centres may bias the results. However, given the sample size and the baseline characteristics of the study population, we believe the model is useful and can be extrapolated.[27]

Other factors such as variables related to health and social status could be risk factors of admission.[28–30] The inclusion of

these variables would have improved the predictive ability of the model. However, this information is not recorded in our database.

Knowing the risk factors of hospital admission, one important area for future research is to validate the interventions designed to prevent and reduce hospital readmissions. It would be of great interest to do a cohort study to compare the interventions in terms of health and economic outcomes. The study results would help us to determine whether the interventions are cost-effective.

CONCLUSION

In conclusion, the model developed in this study may be useful in daily practice for identifying HIV patients who are at high risk of hospital admission.

What this paper adds

What is already known on this subject

- An ageing HIV population demands a new approach to the management of HIV infection.
- There are currently several methods to predict unplanned hospital admissions in patients with chronic diseases, but to date there is no model targeted to predict the 1-year risk of admission among the HIV population.

What this study adds

- This is the first study to present a mathematical model for predicting the risk of hospital admission within 1 year in the HIV population that is under highly active antiretroviral treatment (HAART).
- The predictive model for 1-year hospital admission in HIV patients appears to be a good way to stratify and subsequently identify patients who need further evaluation.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study design was approved by the local ethics committees of the participating study site. (0009/13).

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