**DEVELOPMENT AND VALIDATION OF A RISK PREDICTION MODEL OF LINEZOLID-INDUCED THROMBOCYTOPENIA**

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**Background**

* **First paragraph:** introduction about linezolid and associated ADR including thrombocytopenia
* **Second paragraph:** what is already known in the literature about this association (magnitude and associated factors)
* **Third paragraph:** the importance of investigation this association in Vietnamese settings and develop a risk prediction model. Why is this study needed?

This study aimed to develop and validate risk prediction model of linezolid-induced thrombocytopenia adapted to Vietnamese setting. In addition, we constructed a simplified risk score using this model to enhance the applicability of the prediction rule in clinical practice.

**Methodology**

**Study design and data sources**

We conducted a retrospective, multicentric, cohort study using data collected from three hospitals in Northern Vietnam (Bach Mai Hospital, Thanh Nhan Hospital and National Hospital of Tropical Diseases).

Ethical approval was obtained from xxx.



**Study population**

We retrieved medical health records of all adult patients admitted to the hospitals during specific periods (Bach Mai Hospital: November 1st to December 31st 2019, December 1st 2022 to March 31st 2023, Thanh Nhan Hospital: January 1st to June 30th 2020, September 1st 2022 to February 28th 2023, and National Hospital of Tropical diseases: July 1st to December 31st 2021, April 1st to September 30th 2022). Patients were included in this study if they met all the following inclusion criteria: ≥ 18 years old, were prescribed linezolid during their hospitalization for at least 3 days and had record of platelet count before or after linezolid treatment. Each patient was included only once per adminission and the first linezolid treatment course was evaluated. Included patients were followed up until the end of the linezolid treatment course or discharge date whichever comes first.

**Exposures**

**Outcomes**

Linezolid-induced thrombocytopenia (LI-TP) was defined as a reduction of platelet count to < 112.5 G/L (75% of the lower limit of normal) for patients whose baseline platelet counts were in the normal range. For patients with baseline platelet count below the lower limit of normality (< 150 G/L), linezolid-induced thrombocytopenia was defined as a decrease in platelet count of ≥ 25% from the baseline value. Of note, the normal range of platelet count is 150 – 450 G/L.

**Predictors**

Patient characteristics in the train set: age, sex, weight, clinical department, comorbidities, invasive interventions, types of infection, baseline laboratory tests, comedications.

* Linezolid therapy: duration, route, dose
* Characteristics of thrombocytopenic adverse event:

+ Number and percentage of patients with LI-TP in the train set

+ The latent period of LI-TP

+ Severity of adverse event according to CTCAE scale

* Risk factors associated with LI-TP in univariate and multivariate logistic regression analyses
* Internal validation of the risk prediction model:…

**Data analyses**

3. Definition of variables

Patient’s platelet count values were recorded from 7 days before starting linezolid to hospital discharge. The number of days to the first thrombocytopenic platelet value and the lowest platelet value were recorded and assessed.

Laboratory test results were considered baseline if they were collected at the start of the linezolid treatment to 7 days prior (choose the closest date to linezolid start date as baseline).

Patient’s creatinine clearance (CLCR) was calculated by the Cockcroft-Gault formula in which the patient’s serum creatinine and weight was collected at the start of linezolid treatment.

With gender factor=1 for male and 0.85 for female

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Renal function was classified as follows: stage 1 (CLCR ≥ 90 ml/min), stage 2 (60 ≤ CLCR < 90), stage 3 (30 ≤ CLCR < 60), stage 4 (15 ≤ CLCR < 30) and stage 5 (CLCR < 90). The severity of LI-TP was assessed based on nadir platelet count using CTCAE scale as follows: xxxx.







Statistical analysis plan

* The time from the start of linezolid treatment to the occurrence of linezolid-induced thrombocytopenia was evaluated using the Kaplan–Meier method.
* p values less than 0.05 were considered significant.

Data were analyzed using the software R version 4.3.2.

Development and assessment of the logistic regression model

Logistic regression was used to assess the associations between predictors and LI-TP. The development of our prediction model and risk score followed four steps:

* Development of a risk prediction model

+ Univariate logistic regression analysis was used to select the predictors of the regression model.

+ Multicollinearity between variables was examined using the variance inflation factor (VIFs).

+ Selecting the optimal model based on Bayesian Model Averaging

+ Independent risk factors from multivariate analysis were incorporated to construct a logistic regression model for predicting the occurrence of LI-TP.

Model performance: Predictive accuracy of the final model was assessed by calibration and discrimination parameters: Discrimination was estimated by the area under the receiver operating characteristic curve (AUC) (0.5 indicates no discrimination - 1.0 indicates perfect discrimination); Calibration was assessed visually with a calibration plot and formally using the Hosmer-Lemeshow goodness-of-fit test (p > 0.05 indicates good fit)

Internal validation: The model was internally validated using a nonparametric bootstrap approach (1000 samples). The model’s over-optimism (when applied to new patients in a similar population) was measured by the AUC difference between the bootstrap samples (average AUC) and the original full sample.

Risk score construction: A simplified risk score was constructed based on the hierarchy of the regression coefficients in the final model (each coefficient was divided by the smallest coefficient and rounded to the nearest integer). The score’s predictive performance (AUC) was assessed and compared with that of the original model. Risk of thrombocytopenia corresponding to each score was calculated and grouped into four categories: “low” (<5%), “moderate” (5%–25%), “high” (25%–75%) and “very high” (>75%).

### 3.2. Choosing covariates for multivariate analysis

Covariates with P < 0.1 in univariate analysis were included in the multivariate analysis, and the final independent predictors identified using backward elimination procedures.

**DATA DICTIONARY**

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| --- | --- | --- | --- |
| **Variable name** | **Format** | **Description** | **Values** |
| patient\_ID | char | Record number, patient | character strings |
| site | varchar (3) | Hospital’s name and data collection phase | 2 characters followed by a number  BM: Bach Mai Hospital  TN: Thanh Nhan Hospital  ND: National hospital for Tropical Diseases  1, 2: number of data collection phase |
| **A. Demographic data** |  |  |  |
| patient\_name | char | Patient’s name | character strings |
| patient\_age | number (1) | Patient’s age at time of using linezolid | integer |
| patient\_sex | number (1) | Patient’s gender | 0 = Male, 1 = Female |
| patient\_weight | number (2, 1) | Patient’s weight at time of using linezolid | kg |
| charlson | number (1) | Charlson score | integer |
| dept | char | Name of clinical department prescribed linezolid | character strings |
| dept\_ICU | number (1) | ICU admittance at time of using linezolid | 1 = Yes |
| dept\_ER | number (1) | ER admittance at time of using linezolid | 1 = Yes |
| dept\_other | number (1) | Other departments admittance at time of using linezolid | 1 = Yes |
| **B. Comorbidities** | | | |
| comorb\_HTN | number (1) | Hypertensive | 1 = Yes |
| comorb\_DM | number (1) | Diabetes mellitus type 2 | 1 = Yes |
| comorb\_HF | number (1) | Heart failure | 1 = Yes |
| comorb\_angina | number (1) | Angina | 1 = Yes |
| comorb\_cirr | number (1) | Cirrhosis | 1 = Yes |
| comorb\_COPD | number (1) | Chronic obstructive pulmonary disease | 1 = Yes |
| comorb\_CVA | number (1) | Cerebrovascular accident | 1 = Yes |
| comorb\_MI | number (1) | Myocardial infarction | 1 = Yes |
| comorb\_K | number (1) | Malignancy diseases | 1 = Yes |
| comorb\_hematological | number (1) | Hematological diseases | 1 = Yes |
| **C. Invasive interventions at time of linezolid administration** | | | |
| invasive\_ETI | number (1) | Endotracheal tube | 1 = Yes |
| invasive\_CVC | number (1) | Central venous catheter | 1 = Yes |
| invasive\_IHD | number (1) | Intermittent hemodialysis | 1 = Yes |
| invasive\_CRRT | number (1) | Continuous renal replacement therapy | 1 = Yes |
| **D. Clinical tests before using linezolid** | | | |
| baseline\_date | date | Date of clinical test | yyyy-mm-dd |
| baseline\_CLCR | number (?) | Creatinine clearance | decimal |
| baseline\_HGB | number (3) | Hemoglobin count | integer |
| baseline\_WBC | number (?) | White blood cell count | decimal |
| baseline\_PLT | number (3) | Platelet count | integer |
| **D. Types of infection at time of linezolid administration** | | | |
| infect\_sepsis | number (1) | Septic shock | 1 = Yes |
| infect\_CAP | number (1) | Community-acquired pneumonia | 1 = Yes |
| infect\_HAP | number (1) | Hospital-acquired pneumonia | 1 = Yes |
| infect\_SSTI | number (1) | Skin and soft tissue infection | 1 = Yes |
| infect\_CNS | number (1) | Central nervous system infection | 1 = Yes |
| infect\_IAI | number (1) | Intra-abdominal infection | 1 = Yes |
| infect\_UTI | number (1) | Urinary tract infection | 1 = Yes |
| infect\_BJI | number (1) | Bone and joint infection | 1 = Yes |
| infect\_septicemia | number (1) | Septicemia | 1 = Yes |
| **E. Linezolid treatment** | | | |
| LZD\_start | date | First day of using linezolid | yyyy-mm-dd |
| LZD\_end | date | Last day of using linezolid | yyyy-mm-dd |
| LZD\_duration | number (2) | Duration of linezolid administration | days |
| LZD\_route | char | Linezolid route of administration | IV: intravenous route  PO: oral route  IV&PO : both intravenous and oral administration |
| LZD\_dose\_per\_weight | number (2,2) | Daily dose of linezolid per weight | decimal |
| **F. Comedications during linezolid treatment** | | | |
| comed\_aspirin | number (1) | Use of aspirin | 1 = Yes |
| comed\_aceclofenac | number (1) | Use of aceclofenac | 1 = Yes |
| comed\_diclofenac | number (1) | Use of diclofenac | 1 = Yes |
| comed\_ibuprofen | number (1) | Use of ibuprofen | 1 = Yes |
| comed\_naproxen | number (1) | Use of naproxen | 1 = Yes |
| comed\_paracetamol | number (1) | Use of paracetamol | 1 = Yes |
| comed\_penicillin | number (1) | Use of penicillin | 1 = Yes |
| comed\_cepha | number (1) | Use of cephalosporin | 1 = Yes |
| comed\_carbapenem | number (1) | Use of carbapenem | 1 = Yes |
| comed\_cotrimoxazol | number (1) | Use of cotrimoxazol | 1 = Yes |
| comed\_vancomycin | number (1) | Use of vancomycin | 1 = Yes |
| comed\_levofloxacin | number (1) | Use of levofloxacin | 1 = Yes |
| comed\_daptomycin | number (1) | Use of daptomycin | 1 = Yes |
| comed\_teicoplanin | number (1) | Use of teicoplanin | 1 = Yes |
| comed\_ethambutol | number (1) | Use of ethambutol | 1 = Yes |
| comed\_pyrazinamid | number (1) | Use of pyrazinamid | 1 = Yes |
| comed\_rifampin | number (1) | Use of rifampin | 1 = Yes |
| comed\_cetirizin | number (1) | Use of cetirizin | 1 = Yes |
| comed\_heparin | number (1) | Use of heparin | 1 = Yes |
| comed\_clopidogrel | number (1) | Use of clopidogrel | 1 = Yes |
| comed\_enoxaparin | number (1) | Use of enoxaparine | 1 = Yes |
| comed\_dexamethason | number (1) | Use of dexamethasone | 1 = Yes |
| comed\_amiodaron | number (1) | Use of amiodarone | 1 = Yes |
| comed\_furosemid | number (1) | Use of furosemide | 1 = Yes |
| comed\_simvas | number (1) | Use of simvastatin | 1 = Yes |
| comed\_bisoprolol | number (1) | Use of bisoprolol | 1 = Yes |
| comed\_diltiazem | number (1) | Use of diltiazem | 1 = Yes |
| comed\_eptifibatid | number (1) | Use of eptifibatid | 1 = Yes |
| comed\_quinidin | number (1) | Use of quinidin | 1 = Yes |
| comed\_haloperidol | number (1) | Use of haloperidol | 1 = Yes |
| comed\_valproic | number (1) | Use of valproic acid | 1 = Yes |
| comed\_carbamazepin | number (1) | Use of carbamazepine | 1 = Yes |
| comed\_phenytoin | number (1) | Use of phenytoin | 1 = Yes |
| comed\_mirtazapin | number (1) | Use of mirtazapine | 1 = Yes |
| comed\_quetiapin | number (1) | Use of quetiapine | 1 = Yes |
| comed\_ondansetron | number (1) | Use of ondansetron | 1 = Yes |
| comed\_palonosetron | number (1) | Use of palonosetron | 1 = Yes |
| comed\_oseltamivir | number (1) | Use of oseltamivir | 1 = Yes |
| comed\_quinin | number (1) | Use of quinin | 1 = Yes |
| comed\_pembrolizumab | number (1) | Use of pembrolizumab | 1 = Yes |
| comed\_trastuzumab | number (1) | Use of trastuzumab | 1 = Yes |
| comed\_atezolizumab | number (1) | Use of atezolizumab | 1 = Yes |
| comed\_durvalumab | number (1) | Use of durvalumab | 1 = Yes |
| comed\_IVIG | number (1) | Use of IVIG | 1 = Yes |
| comed\_tacrolimus | number (1) | Use of tacrolimus | 1 = Yes |
| comed\_fluorouracil | number (1) | Use of fluorouracil | 1 = Yes |
| comed\_irinotecan | number (1) | Use of irinotecan | 1 = Yes |
| comed\_leucovorin | number (1) | Use of leucovorin | 1 = Yes |
| comed\_oxaliplatin | number (1) | Use of oxaliplatin | 1 = Yes |
| **G. Clinical tests during hospital stay** | | | |
| test\_date | date | Date of clinical test | yyyy-mm-dd |
| test\_HGB | number (3) | Hemoglobin count | integer |
| test\_WBC | number (?) | White blood cell count | decimal |
| test\_PLT | number (3) | Platelet count | integer |
| test\_ADR\_TP | number (1) | Thrombocytopenia occurrence | 1 = Yes, 0 = No |
| test\_CTCAE | number (1) | Severity of thrombocytopenia according to CTCAE scale | Platelet count (G/L):  1: 75 – 150  2: 50 – 75  3: 25 – 50  4: < 25 |
| test\_onset | number (2) | Days from the start of linezolid administration to thrombocytopenia occurrence | days |