A Substitutional Clinical Nomogram Model for Medical Thoracoscopy to Identify Tuberculous Pleural Effusion

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Research

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Abstract

Background: Tuberculous pleural effusion (TPE) is one of the most prevalent causes of exudative pleural effusion. As it is curable, early diagnosis is essential. Nevertheless, direct examination is not so sensitive while thoracoscopy is invasive and resource-demanding.

Objective: To seek a less-invasive but also cost-effective substitute for medical thoracoscopy to identify TPE.

Methods: We retrospectively collected 662 patients with pleural effusions who have undergone thoracoscopy as the training cohort, developed a predictive model and then validated it in another independent cohort. Independent predictor was screened by univariate analysis, feature selection and multivariate logistic regression. A predictive nomogram model was then established and evaluated by calibration, discrimination and clinical values. A standard model with a pleural adenosine deaminase (plADA) cut-off value at 40 IU/L was applied for comparison.

Results: A lower plADA threshold at 24.5 IU/L was identified to discriminate TPE from other etiologies. Furthermore, serum tumor marker CA153 and Cyfra21.1, pleural lactic acid dehydrogenase and pleural interstitial cells were also identified as independent predictors ($p<0.05$) in multivariate logistic regression. The multivariate nomogram model presented good calibration, discrimination and clinical values, superior to the standard model. Excellent discrimination was demonstrated by the Harrell's concordance index of 0.993 in the training cohort and 0.968 in the validation cohort. Furthermore, decision curve analysis demonstrated that the multivariate nomogram model added more benefit to patients with TPE.

Conclusion: A multivariate nomogram model involved biochemical examinations and thoracentesis performed well in TPE clinical diagnosis among undetermined pleural effusions with approximate efficacy to medical thoracoscopy.

Introduction

Tuberculous pleurisy is one of the most prevalent causes of exudative pleural effusions, especially in areas with high incidence [1, 2]. However, the therapy and prognosis are totally different in different diseases although they may present similar manifestations. Tuberculous pleural effusion (TPE) is curable and early diagnosis is essential for its management and control [3, 4]. Nevertheless, it is not so sensitive to directly find mycobacteria due to its scarcity nature in the fluid. It is believed that it's the delayed hypersensitivity rather than direct stimulation of mycobacteria that plays an important role in its pathology [5, 6]. Pleura biopsy through thoracoscopy procedure improvs the diagnosis accuracy but it is also more invasive and resource-demanding [7, 8]. As the most common extrapulmonary tuberculosis [8], TPE is usually more prevalent in some low-income areas where the gap between diagnosis and treatment is larger, highlighting the significance of establishing an effective clinical diagnostic model based on less-invasive examination such as thoracentesis and pleural effusion analysis. This study aimed to explore a

simpler predictive model to tell TPE from other etiologies of pleural effusions with approaching accuracy to thoracoscopy.

Methods

Study design and subjects

This was a retrospective cohort study comparing the clinicopathological characteristics between TPE group and Non-TPE group.

A total of 853 patients with pleural effusions who have undergone thoracoscopy and were diagnosed in Xinqiao Hospital were enrolled (training cohort with 662 patients from January 2013 to December 2016 and validation cohort with 191 patients from January 2017 to August 2018). As plADA was known to be the most effective predictor in clinical diagnosis, patients without plADA measurement were excluded. Recruitment pathway was presented in Fig. 1 and diagnostic criteria were in Appendix S1. The inclusion and exclusion criteria were listed below.

Inclusion criteria: 1.18-80 years old; 2. Patients with pleural effusion indicated by Chest physical examination, ultrasound, CT or other imaging examinations; 3. Patients who had undergone thoracoscopy in Xinqiao Hospital during January 2013 to August 2018 and were diagnosed. Exclusion criteria: 1. Patients who had known etiologies before thoracoscopy examination. 2. Patients who did not perform pleural effusion ADA (plADA) analysis or such data was missing.

Clinical Examinations

Thoracoscopy and tissue biopsy were performed using Olympus LTE-240. Biochemistry examinations were performed by automatic analyzers. Tumor markers were tested in electroluminescence method (ABBOTT/ i2000). Adenosine deaminase (ADA) and lactate dehydrogenase (LDH) were both analyzed in rate method (BECKMAN/ AU5800). Pleural effusion cell classification was performed through nucleic acid fluorescence staining and laser flow analysis (Hisenmicon/ XS-1000i). The monocytes and polykaryocytes mainly indicated lymphocytes and granulocytes respectively as interstitial cells presented pleural mesothelia. Erythrocyte sedimentation rate (ESR) was analyzed in Westergren method (YHLO/ Vision-C). Fever was defined as body temperature above 37.3°C when admitted in the hospital.

Model development and validation

Clinicopathological characteristics were analyzed by univariate chi-square test or nonparametric Mann–Whitney U-test and missing data was completed through multiple imputation. Univariate analysis also included boxplot presentation (Supplement Fig. S1a, b), receiver operation curve (ROC) analysis (Supplement Fig. S1c) and correlation analysis (Supplement Fig. S1d). Before model development, the data out of the 1–99% range of dataset was replaced by the 1% quantile or 99% quantile value. The least absolute shrinkage and selection operator (LASSO) method was then used to select the most useful predictive factors. Those factors were then included in multivariate logistic regression and a nomogram

model was established according to their respective coefficients. The Harrell's concordance index (C-index) and calibration curves were used to evaluate discrimination and goodness of fit respectively. Decision curve analysis was used to evaluate clinical usefulness. A standard binary determination model with plADA cut-off value at 40 IU/L was applied for comparison.

Statistical analysis

Statistical analysis was performed with R software (version 3.6.2; http://www.Rproject.org). The packages in R used in this study were reported in Appendix S2. The reported statistical significance levels were all two-sided with statistical significance set at $p < 0.05$.

Results

Clinical characteristics

662 patients with TPE (n = 286) or Non-TPE (n = 376) were included in the retrospective training cohort while 191 patients with TPE (n = 75) or Non-TPE (n = 116) were involved in the validation cohort. The clinical characteristics of both training cohort and validation cohort were showed in Table 1. The two cohorts were independent and without significant difference in TPE incidence ($p = 0.375$). As missing data was completed by imputation, clinicopathological information was compared between cases with or without missing data in the training cohort (Supplement Table. S1). Those with missing data were younger and had higher TPE rate as many young participants who were suspicious of TPE didn't undergo serum tumor marker assessment.

Development of a predictive model

LASSO reduced data dimension (Fig. 2a, b) and 7 factors, serum tumor marker CA153 and Cyfra21.1, bloody pleural effusion, plADA, pleural carcinoembryonic antigen (plCEA), pleural lactic acid dehydrogenase (plLDH) and pleural interstitial cells (plInterstitial) were left. Multivariate logistic regression was then performed and CA153, Cyfra21.1, plADA, plLDH and plInterstial were further identified as independent predictors($p < 0.05$), with respective coefficients of -2.52, -5.10, 4.84, -1.72 and −0.86. Based on multivariate logistic regression, a multivariate nomogram model involved those 5 independent predictors was developed (Fig. 2c, d).

Performance and validation of nomogram

In the training cohort, the calibration curve of the multivariate nomogram model showed excellent consistence between predicted risk and observed frequency of TPE in the training cohort (Fig. 3a). Hosmer-Lemeshow goodness of fit test suggested no significant unfit of multivariate nomogram ($p = 0.6$). The C-index used to evaluate the accuracy of the multivariate nomogram model was 0.993 (95% CI, 0.989 to 0.997) in the training cohort (Fig. 3a) and 0.968 (95% CI, 0.940 to 0.996) in the independent validation cohort (Fig. 3b), better than plADA40 model with the C-index of 0.852 (95% CI, 0.825 to 0.879) and 0.78 (95% CI, 0.722 to 0.838) in the two cohorts respectively.

Clinical use

The decision curve analysis (Fig. 4) demonstrated that multivariate nomogram model performed better than plADA40 model, the treat-all-patients scheme or the treat-none scheme, indicating the multivariate nomogram model added more benefit than plADA40 model.

Discussion

This study firstly applied a quantified nomogram predictive model in TPE and the multivariate nomogram model was demonstrated to be efficient in resource-limited conditions. The model is also easy to use as it enables practitioners to input examination results and predict TPE risk in R software using “DynNom” package. It is meaningful to establish such an efficient and less invasive but also practicable model for clinical TPE diagnosis as thoracoscopy and pathological diagnosis are source-demanding and the direct diagnostic examination is not so sensitive, especially in areas where the tuberculosis load is high.

The direct diagnostic examination, which includes mycobacterium tuberculosis culture, acid fasting staining and nucleic acid examination, has a low sensitivity as mycobacteria is scarce in TPE [9, 10]. Correspondingly, all the mycobacteria culture and acid fasting staining of tuberculous pleural effusion was negative in this study. Nucleic acid amplification test (NAAT) was reported to be more sensitive[11] but still relied on thoracoscopy to provide sufficient biopsy sample.

However, there were scarce quantified models to predict TPE. A study in 2003 reported 2 models with high efficacy. One involved 4 variables, plADA(≥ 40 U/L, 5 points), age (≤ 35 yrs, 2 points), temperature (≥ 37.8°C, 2 points) and pleural red blood cells (≤ 5×10^9/L, 1 point) while another compromised 6 elements, history of malignancy (none, 3 points), age (≤ 35 yrs, 2 points), temperature (≥ 37.8°C, 2 points), pleural red blood cells (≤ 5×10^9/L, 1 point), pleural protein (≥ 50 g/L, 1 point) and pleural fluid to serum LDH ratio (≥ 2.2, 1 point)[12]. High sensitivity and specificity though it reported, about 25% still remained unclear. Similarly, another study in 2011 proposed a scoring model, including seven risk factors, temperature (> 38°C ,1.0 point), tuberculin test (positive, 1.0 point), C-reactive protein (≥ 26 mg/L, 1.5 points), pleural fluid lymphocyte percentage (≥ 85%, 1.0 point), pleural fluid protein (≥ 49 g/L, 1.0 point), pleural fluid adenosine deaminase (≥ 43 U/L, 2.5 points) and serum and/or pleural fluid mycobacterium tuberculosis antibody (positive, 2.0 points)[13]. However, those scores for every predictor seemed to be given randomly.

Tumor markers are important tests to exclude malignant pleural effusions as malignancy and tuberculosis are both the major etiologies of exudative pleural effusion. In this study, CA153 and Cyfra21.1 were both included as negative predictors in multivariate nomogram model. CA153 is a glycan-related biomarker and its increasement in serum has been established as a biomarker for both breast and ovarian cancer diagnosis since 1980s [14]. It was also reported that serum CA153 was also a gorgeous indicator for lung cancer, lymphoma and some other noncancer diseases in a study involved 19,789 healthy individuals and patients [15]. Cyfra21-1, cytokeratin 19 fragments, has also been demonstrated to

be the most sensitive tumor marker in non-small cell lung cancer, particularly the squamous cell type [16]. PlCEA was also believed to be a highly specific tumor marker associated with MPE [17, 18] but was excluded by multivariate logistic regression possibly due to collinearity with other predictors.

Thoracentesis and pleural effusion analysis are less-invasive and easier to perform than thoracoscopy or percutaneous lung biopsy.

ADA is a ubiquitous enzyme to deaminate adenosine and 2-deoxyadenosine, with highest activity in lymphoid tissues [19]. It plays a key role in adenosine homeostasis and thus immunomodulation [20]. Besides inside the cells, it also presents on the cell surface and could trigger T-cell coactivation. Furthermore, it was reported that it could potentiate CD4 + T-cell differentiation and proliferation, including effector T cells, memory T cells and regulatory T cells [21].

It has been widely reported that the elevated ADA activity in pleural effusion was an efficient biomarker of TPE, with a commonly used cut-off value at 40 IU/L. As a recent meta-analysis reported, 40 IU/L was more suitable to be an excluding threshold rather than confirmation while the diagnostic utility of plADA cut-off value depended on the geographical regions and clinical backgrounds [22]. In Brazil, where tuberculosis prevalence was reported to be about 0.077% and TPE accounted for approximately 50% in all etiologies, a meta-analysis also suggested 40 IU/L as an excluding threshold and a lower cutoff value at about 30IU/L accompanied by other examinations may be superior [23]. Correspondingly, 35 IU/L was also more recommended in Spanish [24]. It was also implied that growing threshold value couldn't remarkably improve diagnostic performance once over 40 IU/L in an India meta-analysis [25]. This study proposed a cut-off value at 24.5 IU/L through univariate ROC analysis, which was lower than most commonly used value but closer to results mentioned above. Comparably, a recent study in China also recommended a lower threshold, as half of TPE showed plADA value below 40 IU/L [26]. Meanwhile, a Hongkong research recommended 26.5 IU/L as a TPE threshold when plADA level was less than 100 IU/L if without evidence of malignancy and non-tuberculous infection [27]. Similarly, a Taiwan study in which included lymphocyte-dominant exudative pleural effusions also indicated a threshold of 30 IU/L to differentiate TPE from MPE as the Asian population had lower ADA [28]. Taken together, a lower cut-off value of plADA may be more acceptable in Asian population to discriminate TPE from others, which also remains to be further investigation.

However, elevated plADA can also occur in many other etiologies, such as neutrophilic effusions, lymphomas and rheumatic inflammation [29–32]. Meanwhile, it can also be lower in older or critically ill groups [33]. Accordingly, combination with other tests is necessary for more accurate diagnosis.

LDH is an essential metabolic enzyme found in nearly all living cells. It was reported that plLDH was significantly higher in MPE or parapneumonic pleural effusions [34–36] than TPE, which was consistent with this study.

Interstitial cells in the pleural effusion may reveal the pleural mesothelium apoptosis or necrosis. The higher percentage in Non-TPE group may related to more invasiveness of malignant and infectious

diseases than tuberculous delayed hypersensitivity.

Medical thoracoscopy is usually performed after thoracentesis implying no definite diagnosis. however, it is also resource-demanding and more invasive. Combining above 5 independent predictors, the multivariate nomogram model performed approximate accuracy to thoracoscopy (622/632) in the training cohort. Furthermore, it indeed added more benefit for patients with TPE than commonly used plADA40 model.

However, there were also some potential limitations. Firstly, the retrospective nature leaved some information inaccessible and there were about 16.3% (109/662) cases with missing data in training cohort although multiple imputation was performed and clinicopathological information comparison between patients with or without part data not available showed no significant difference in most clinicopathological characteristics (Supplement Table. S1) and LASSO selected the same 7 factors in primary completed cohort as imputed completed cohort. Secondly, participants recruited were from a university hospital rather than multiple centers, which leaved the model to be further tested or adjusted in other centers.

Conclusions

In summary, it is feasible to establish an effective and clinically useful model to discriminate TPE from other etiologies of pleural effusions based on less invasive and easier examinations. The nomogram model based on CA153, Cyfra21.1, plADA, plLDH and plInterstial through biochemistry examination and diagnostic thoracentesis showed approximate accuracy to more invasive thoracoscopy.

Abbreviations

TPE: tuberculous pleural effusion; Non-TPE: not the tuberculous pleural effusion; CEA: carcinoembryonic antigen; ADA: adenosine deaminase; LDH: lactic acid dehydrogenase; plCEA: pleural carcinoembryonic antigen; plADA: pleural adenosine deaminase; plLDH: pleural lactic acid dehydrogenase; plInterstitial: pleural interstitial cells; ROC: receiver operation curve; C-index: The Harrell's concordance index; LASSO: the least absolute shrinkage and selection operator; NAAT: Nucleic acid amplification test; plADA40: cut-off value of pleural adenosine deaminase is 40IU/L.

Declarations

Ethics approval and consent for participation

The retrospective analysis was ethically approved by the institutional review board of Xinqiao Hospital and the informed consent requirement was waived.

Acknowledgements

None.

Authors' contributions

Ye Fan designed this study and took responsibility for the integrity of the data. Jie-Ru Guo was responsible for data analysis and drafting the manuscript. Jing Zhang, Xian-Li Wu, Zan-Sheng Huang, Ming-zhou Zhang, Wan-Lei Fu and Ping-Wang contributed to data collection and preparation of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data can be shared through reasonable request to corresponding author.

Consent for publication

Not required due to study design.

Competing interests

The authors have no conflicts of interest to declare.

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Table

Due to technical limitations, table 1 xlsx is only available as a download in the Supplemental Files section.

Figures

Figure 1

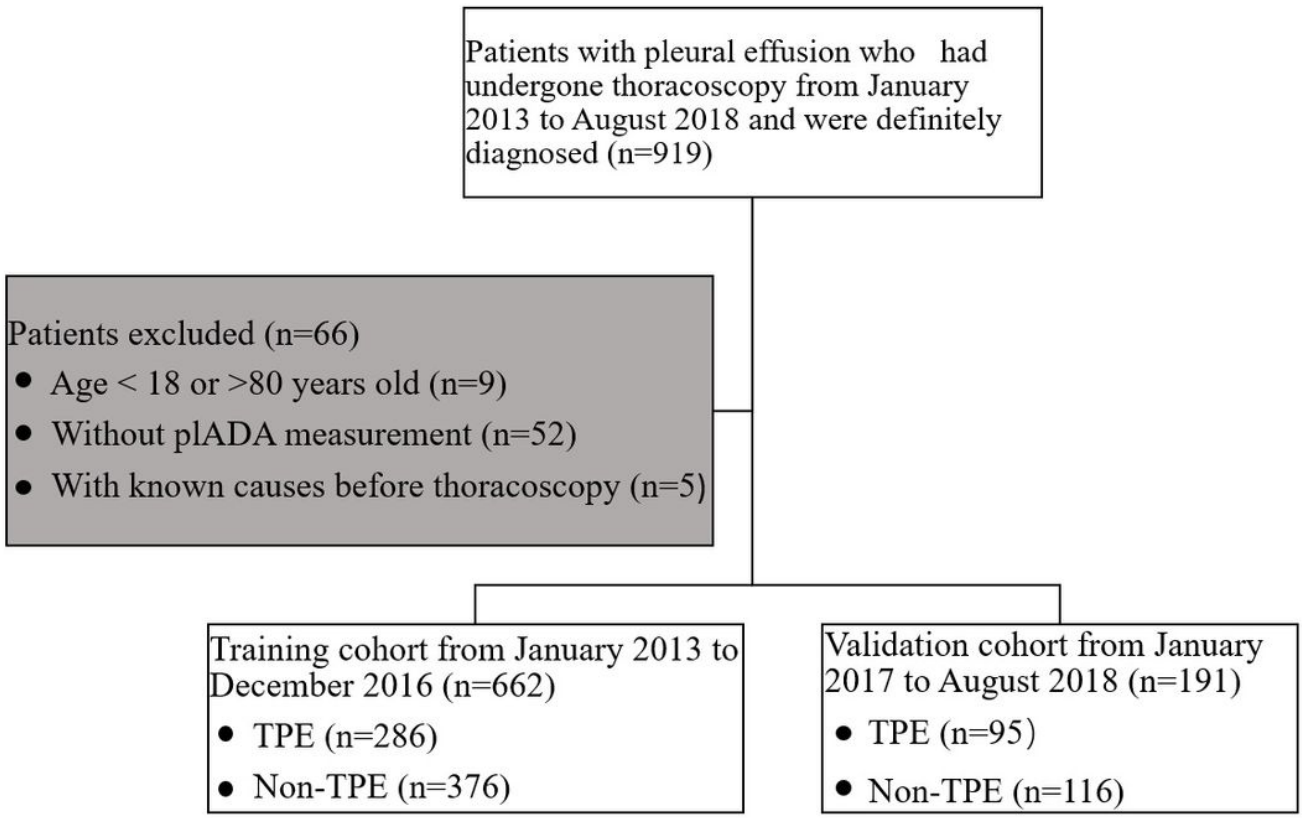

Figure 1

Recruitment pathway of participates. TPE, tuberculous pleural effusion; plADA, pleurl adenosine deaminase.

Figure 2

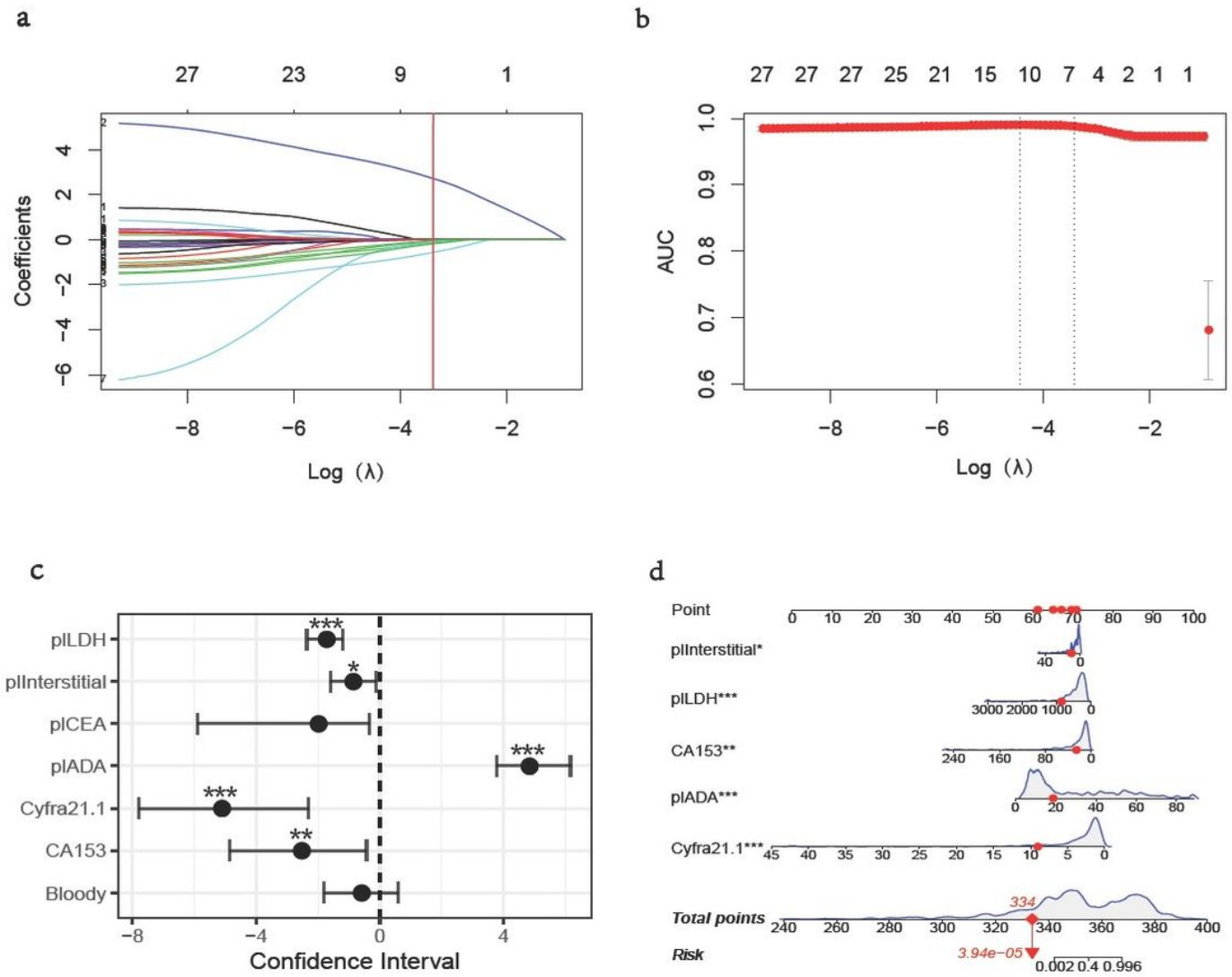

Figure 2

Predictor selection and model establishment. The least absolute shrinkage and selection operator (LASSO) binary logistic regression was performed and a coefficient profile plot was produced against the log (λ) sequence. Vertical line was drawn at the value selected using 10-fold cross-validation, where an optimal λ value of 0.0326 (1-SE criteria), with log (λ), -3.42 was chosen according to 10-fold cross-validation (a). The area under the receiver operating characteristic (AUC) curve was plotted versus log(λ) for 10-fold cross-validation (b). Multivariate logistic regression selected 5 independent predictors, CA153, Cyfra21.1, plADA, plLDH and plInterstial, with respective coefficients of -2.52, -5.10, 4.84, -1.72 and -0.86. The black dot stood for the coefficient value as the horizontal bar represents 95% confidence interval (c). Enhanced regression nomogram with covariate distributions superimposed on it was then established based on multivariate logistic regression. The predictive probability of the 220th patient in the training cohort was presented by red solid circles. The symbol * reflected that the factors were significantly

different between TPE group and Non-TPE group as one means that p value was between 0.05 and 0.01, two for between 0.01 and 0.001 and three for below 0.001.

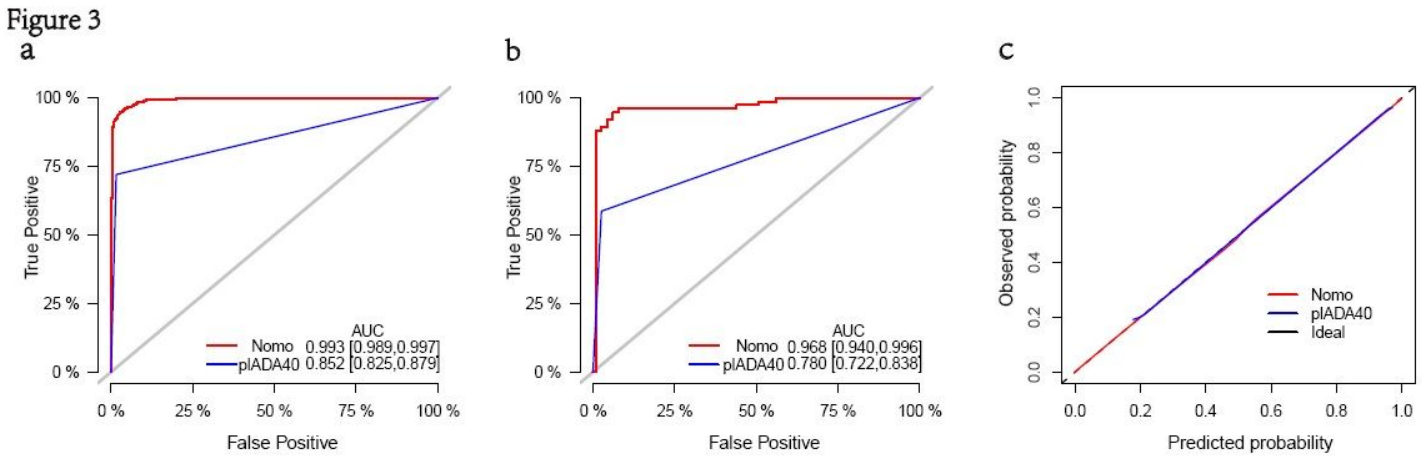

Figure 3

Validation of multivariate nomogram and comparison among nomogram and the standard plADA model with a cut-off value at 40 IU/L (plADA40) both in the training cohort (a) and an independent validation cohort (b). The AUC of the ROC stood for the Harrell's concordance index (C-index), indicating concordance between the observation and prediction. Calibration of nomogram in the training cohort (c) showed good fit and the Hosmer-Lemeshow goodness-of-fit test showed no significant unfit between multivariate nomogram and the ideal fit (p=0.6).

Figure 4

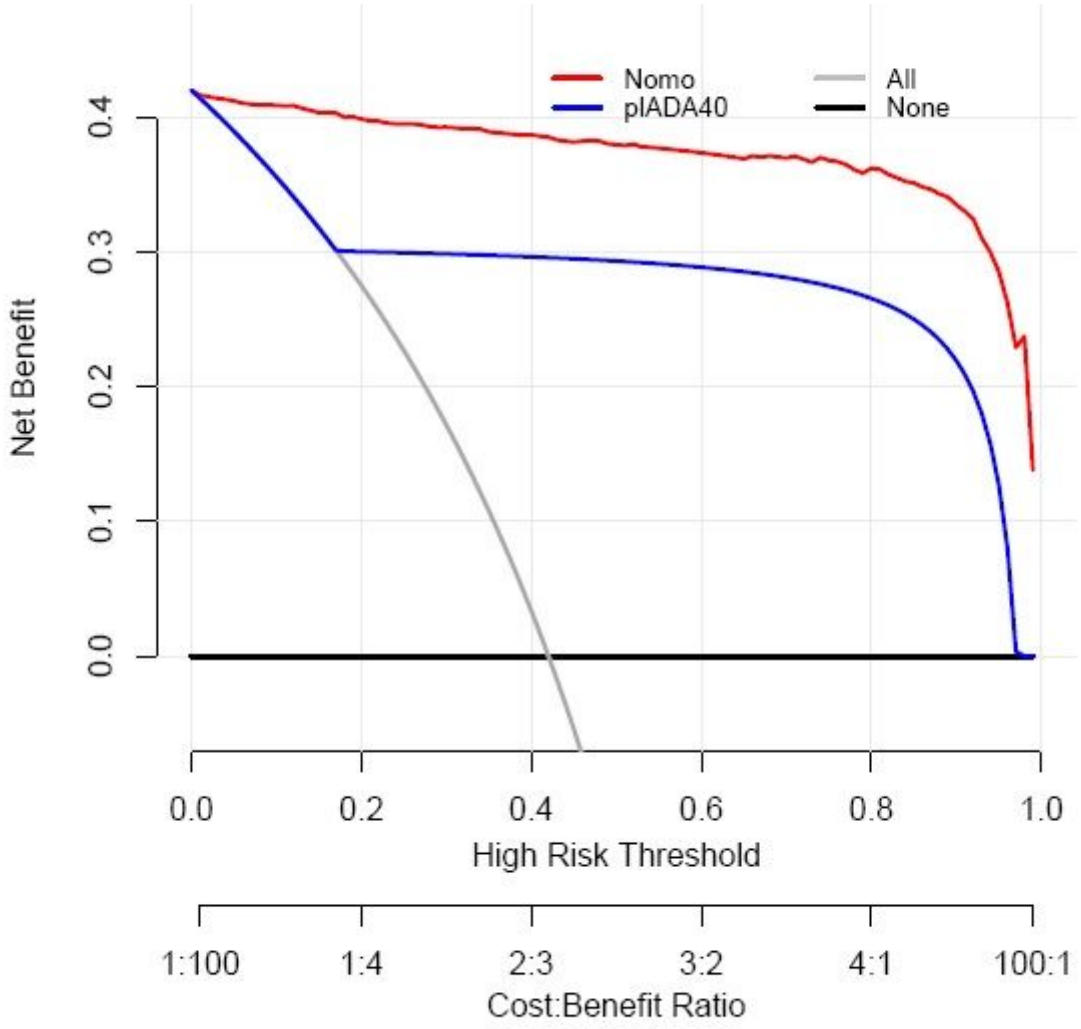

Figure 4

Decision curve analysis of the two models. The y-axis measured the net benefit. The red and blue lines represented the multivariate nomogram and plADA40 model respectively. The gray line represented the assumption that all patients have TPE as the real probability of TPE was set at 0.42 according to this study. The black line represented the assumption that no patients have TPE. The net benefit was calculated by subtracting false positive proportion from true positive proportion, weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment. The decision curve demonstrated that multivariate nomogram performed better.

Supplementary Files

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