Predictive Factors for the Post Embolization Fever after TACE for Hepatocellular Carcinoma Patients: A Single-Center Study in China.

Dan TIAN (tiandan1687@163.com)
Zhongshan Hospital Fudan University https://orcid.org/0000-0002-8511-1054
Xiaoyu LI
Zhongshan Hospital Fudan University
Qianzhou LV
Zhongshan Hospital Fudan University

Research article

Keywords: postembolization fever, hepatic artery embolization, risk factors

Posted Date: September 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-75487/v1

Abstract

Background Fever is one of the main symptoms for post-embolism syndrome (PES). This study aimed to determine and validate a model to predict fever after transcatheter arterial chemoembolization (TACE) in patients receiving platinum as the main regimen.

Materials and Methods Clinical data of HCC patients who underwent TACE with platinum was retrospectively collected in the Fudan University Zhongshan Hospital during January 2016 to January 2018. According to post-TACE medical records, patients were divided into fever group and non-fever group. Predictive factors were selected by multivariate logistic regression. The receiver operating characteristic (ROC) curve were then performed to detect accuracy and discriminative ability of these factors using the derivation cohort and an independent validation cohort.

Results Fevers were detected in 44 of 252 patients. Demographics, laboratory data were statistically similar within fever group and non-fever group. Strongest predictors identified in multivariate logistic regression included lopiodol emulsion dose (OR, 1.081; 95%CI, 1.006-1.162), number of hepatoprotectants (OR, 0.619; 95%CI, 0.419-0.914), K^+ (OR, 2.992; 95%CI, 1.225-7.308), and albumin-bilirubin (ALBI) grade (OR, 2.249; 95%CI, 1.040-4.862). Furthermore, the area under the ROC curve of derivation cohort and validation cohort were 0.798 and 0.874 respectively, which indicated comparative stability and discriminative ability of this model.

Conclusions lopiodol emulsion dose, number of hepatoprotectants, K^+, and ALBI grade are strong predictors for PEF. The multivariate logistic model of these factors shows a discriminative ability to predict PEF in the validation cohort.

Introduction

Hepatocellular carcinoma (HCC), the most frequent type of liver cancer, is now the fourth most common malignant tumor and the third most lethal malignant tumor in China (1). Different from western countries, East Asia had especially suffered from a very large burden of HBV infection (2). As a vital identified risk factor for HCC, hepatitis B virus (HBV) infection has contributed to more than 60% liver cancer deaths and cases in China (3, 4). Besides the first-line curative treatment-liver resection (LR) for HCC, currently, transarterial chemoembolization (TACE) is the main treatment option for unresectable, large/multifocal HCCs without vascular invasion or extrahepatic spread (5). It has been recommended as the preferred treatment for Barcelona Clinic Liver Cancer (BCLC) patients with stage B HCC according to the current European Association for the Study of Liver guidelines (6). However, TACE is associated with transient post-embolization syndrome (PES) with an incidence range from 30–80% (7, 8). It was characterized as fever, unremitting nausea, vomiting, pain in liver region, abdominal distention, and poor appetite (9). Among them, post-embolization fever (PEF) has been considered to reflect extensive tumor necrosis and represent the efficacy of TACE by physicians. Recent studies have also validated that PEF may be associated with tumor size and the use of embolic agents (10–12). However, PEF is less predicted by

clinical biochemical indicators, and the few existing conclusions are inconsistent (11). The aim of this study was to analyze the predictive factors of fever after TACE in patients with HCC who were treated with platinum as the main regimen, and to help clinicians predict PEF.

Materials And Methods

Inclusion and exclusion criteria

Data were retrospectively collected from patients with HCC who underwent TACE in the Zhongshan hospital, Fudan University from January, 2016 to January, 2018. Inclusion criteria included the following: complete medical records and laboratory data for patients before and after TACE, above 14 years old, the survival time of patients above 3 months, no urinary tract, endocardium, pelvic infection in nearly one month, platinum as the main chemotherapeutic regimen in TACE. Excretion criteria included pregnant women or lactating women and had infection and fever before TACE. Besides, another cohort of 115 patients who met the same inclusion and exclusion criteria mentioned above, were separately collected to be the validation cohort.

Data collection

Data were collected and retrieved through hospital information management system. Demographic information and medical records such as name, sex, age, diagnosis, concomitant diseases, operation procedure, combined medication were recorded. All laboratory examinations before and after TACE were recorded, mainly including blood routine, liver and kidney function parameters (such as total bilirubin, (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), serum creatinine (CRE), uric acid (UA), etc.), tumor markers (such as alpha fetoprotein (AFP), carcinoembryonic antigen (CA)) and coagulation indicators (such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), etc.). The method of collecting preoperative laboratory indicators was collecting venous blood samples within 48 hours before operation and sending them for examination in the morning. ALBI grade has been reported to be a new tool for evaluation of hepatic function in HCC patients as compared to the Child-Pugh classification (13). ALBI score was used for grading (≤-2.60 = grade 1, greater than − 2.60 to≤-1.39 = grade 2, greater than − 1.39 = grade 3). The aspartate aminotransferase/platelet count ratio index (APRI, APRI=[AST(IU/L)/upper limit normal]/PLT(× 10^9/L)] × 100), which is thought to be a biomarker of liver fibrosis and cirrhosis(14), was calculated as well.

Statistical analysis

Data are presented as the mean and standard deviation (SD) or numbers and percentages. For continuous variables, the differences between groups was calculated by independent Student's t-test or Mann-Whitney U test. Chi-squared test or Fisher's exact test were applied for categorical variables. Multivariate logistic regression model using forward selection procedure was then constructed to identify

the independent predict factors for PEF. The receiver operating characteristic (ROC) curve were performed to detect accuracy and discriminative ability of the model using the derivation cohort and a separate validation cohort. All the statistics were bilateral test, $P < 0.05$ was statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Statistics 22.0).

Results

Comparison of general data of patients between fever group and non-fever group

A total of 252 patients were collected, including 209 males and 43 females, aged from 18 to 85 years, with an average age of 57.8 ± 11.3 years. The general data of fever group (n = 44) and non-fever group (n = 208) were shown in Table 1. There was no significant difference in demographic characteristics and complications between the two groups ($P > 0.05$). The number of varieties of hepatoprotectants in fever group was lower than that in non-fever group (1.5 + 0.6 vs 2.4 + 1.3, $P = 0.000$). In addition, the amount of iodized oil injected in fever group during TACE was higher than that in non-fever group (10.5 ± 5.5 vs 7.1 ± 4.6, $P = 0.000$).

Table 1
Comparison of demographic and clinical data between two groups before TACE

Variables	Total	Fever cohort (n = 44)	Non-fever cohort (n = 208)	P-value
Age (years)	58.2 ± 11.2	60.0 ± 10.7	57.8 ± 11.3	0.251
Gender (%)	209	39	170	0.378
Male	43	5	38	
female				
Heart rate	77.5 ± 5.8	78.1 ± 6.7	77.4 ± 5.6	0.439
Drink	16(6.3)	3(6.8)	13(6.3)	1.000
Smoke	23(9.1)	7(15.9)	16(7.7)	0.144
Complication (%)				
Hypertension	73(29.0)	17(38.6)	56(26.9)	0.143
Diabetes	30(11.9)	7(15.9)	23(11.1)	0.440
Renal cyst	65(25.8)	10(22.7)	55(26.4)	0.706
History of cholecystectomy	34(13.5)	5(11.3)	29(13.9)	0.810
Gallstone or Cholecystitis	46(18.3)	8(18.2)	38(18.3)	1.000
Schistosomiasis infection	4(1.6)	1(2.3)	3(1.4)	0.538
Hepatits B	179(71.0)	36(81.8)	143(68.7)	0.100
Liver cirrhosis	86 (34.1)	19(43.2)	67(32.2)	0.167
Fatty liver	3(1.1)	0(0.0)	3(1.4)	1.000
Combined medication				
Anti-hepatitis B drugs	81(32.1)	18(40.9)	63 (30.2)	0.213
Fluorouracil	102(40.5)	29(65.9)	73(35.1)	0.000
Hydroxycamptothecin	14(5.6)	0(0.0)	14(6.7)	0.139
Gemcitabine	16(6.3)	2(4.5)	14(6.7)	0.745
Pirarubicin	75(29.8)	16(36.4)	59(28.4)	0.364
Epirubicin	51(20.2)	11(25.0)	40(19.2)	0.411
Raltitrexed	7(2.8)	1(2.3)	6(2.9)	1.000
Irinotecan	3(1.2)	0(0.0)	3(1.4)	1.000

Variables	Total	Fever cohort (n = 44)	Non-fever cohort (n = 208)	P-value
Number of Hepatoprotectants	2.2 ± 1.2	1.5 ± 0.6	2.4 ± 1.3	0.000
Others				
Platinum dose (mg)	109.5 ± 37.6	126.1 ± 33.2	105.9 ± 37.6	0.001
Iopiodol emulsion dose(mL)	7.7 ± 4.9	10.5 ± 5.5	7.1 ± 4.6	0.000
Note: The history of hepatitis includes hepatitis B, hepatitis C and hepatitis E. There are 2 cases of hepatitis C in the febrile group, 1 case of hepatitis E in the febrile group, 1 case of hepatitis C in the non-febrile group and the rest of them are hepatitis B.				

Table 2
Univariate and multivariate logistic regression showing independent factors associated with fever after TACE

Variables	Univariate			Multivariate		
	OR	95%CI	P-value	OR	95%CI	P-value
Iopiodol emulsion dose(mL)	1.134	1.064–1.209	0.000	1.081	1.006–1.162	0.034
Gender	1.744	0.644–4.717	0.274			
Age (year)	1.018	0.988–1.049	0.251			
Hypertension	1.709	0.866–3.373	0.122			
Heart rate	1.022	0.967–1.081	0.437			
Number of Hepatoprotectants	0.509	0.358–0.724	0.000	0.619	0.419–0.914	0.016
Fluorouracil	0.280	0.141–0.555	0.000			
RBC ($\lozenge 10^{12}$/L)	1.248	0.768–2.028	0.371			
Hb (g/L)	1.003	0.986–1.020	0.757			
Hct (%)	0.996	0.972–1.021	0.756			
PLT ($\lozenge 10^{9}$/L)	1.003	0.999–1.006	0.147			
WBC($\lozenge 10^{9}$/L)	1.021	0.973–1.072	0.391			
TBIL (umol/L)	1.029	0.992–1.067	0.126			
DBIL (umol/L)	1.015	0.960–1.074	0.597			
TP (g/L)	1.051	1.001–1.104	0.048			
Alb (g/L)	0.992	0.926–1.063	0.824			
Glb (g/L)	1.075	1.017–1.138	0.011			
A/G	0.327	0.112–0.960	0.042			
ALT (U/L)	1.013	1.004–1.022	0.006			
AST (U/L)	1.013	1.005–1.020	0.001			
ALP (U/L)	1.003	1.000-1.006	0.042			
GGT (U/L)	1.002	1.001–1.004	0.008			
UREA (mmol/L)	1.224	0.995–1.506	0.056			

Variables	Univariate			Multivariate		
CRE (umol/L)	1.011	0.988–1.034	0.367			
UA (umol/L)	1.000	0.996–1.005	0.854			
Na^+ (mmol/L)	1.057	0.963–1.160	0.243			
K^+ (mmol/L)	2.852	1.236–6.580	0.014	2.992	1.225–7.308	0.016
eGFR (mL/min/1.73 m^2)	0.984	0.955–1.013	0.281			
Glu (mmol/L)	0.990	0.865–1.133	0.881			
AFP	2.529	1.304–4.907	0.006	1.000	1.000–1.000	0.025
CEA (ng/mL)	0.998	0.993–1.004	0.499			
PT(s)	1.212	0.921–1.596	0.170			
TT(s)	0.875	0.679–1.128	0.304			
INR	6.871	0.340-139.003	0.209			
APTT (s)	1.013	0.891–1.150	0.848			
FIB (mg/dL)	1.004	1.001–1.006	0.004			
D-D (mg/L)	1.144	0.976–1.341	0.098			
ALBI grade	2.090	1.074–4.068	0.030	2.249	1.040–4.862	0.039
APRI ratio	1.095	0.819–1.465	0.539			

RBC: red blood cell; Hb: hemoglobin; Hct: hematocrit; PLT: platelet; WBC: white blood cell; TBIL: total bilirubin; DBIL: direct bilirubin; TP: total protein; Alb: albumin; Glb: globulin; A/G: albumin / globulin ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; UREA: urea; CRE: UA: uric acid; eGFR: estimated glomerular filtration rate; Glu: glucose; AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; PT: prothrombin time; TT: thrombin time; INR: International Normalization Ratio; APTT: Activated Partial Thromboplastin Time; FIB: Fibrinogen; D-D: D dimer; ALBI: albumin-bilirubin; APRI: aminotransferase/platelet count ratio index.

Independent factors associated with PEF in the derivation cohort

Univariate analysis showed that iopiodol emulsion dose, hypertension, number of hepatoprotectants, fluorouracil, platelet (PLT), total protein (TP), albumin (Alb), albumin / globulin ratio (A/G), ALT, AST, ALP, GGT, UREA, K^+, AFP, fibrinogen (FIB), D-D (D dimer) and Albumin-bilirubin (ALBI) grade may be risk factors for PEF. After multivariate logistic analysis, four factors including iopiodol emulsion dose, number of

hepatoprotectants, K^+, and ALBI grade within 48 hours before operation were positively correlated with fever after TACE. The OR value of iopiodol emulsion dose was 1.081 (95% CI, 1.006–1.162; P = 0.034), K^+ was 2.992 (95% CI, 1.225–7.308; P = 0.016), ALBI grade was 2.249 (95% CI, 1.040–4.862; P = 0.039). The number of hepatoprotectants used before TACE was a protective factor with OR value of 0.619 (95% CI: 0.419–0.914, P = 0.016). ROC curve analysis showed that AUC of iopiodol emulsion dose, number of hepatoprotectants, K^+, ALBI grade and predict model ranged from 0.5 to 0.8, and the Cut-off point was 6.5 mL, 2.5, 4.25 mmol/L, 1.5 respectively (Table 3).

Table 3
ROC curve analysis of predicted factors

Variables	ROC	Cut-off value
Iopiodol emulsion dose (mL)	0.680	6.5
Number of Hepatoprotectants	0.659	2.5
K^+ (mmol/L)	0.614	4.25
ALBI grade	0.582	1.5
predict model	0.798	/

Discussion

TACE exploits the preferential hepatic arterial supply of HCC for targeted delivery and embolizes of the feeding artery branches of HCC by lipiodol emulsion, microspheres, polyvinyl alcohol and gelatin sponge with chemotherapeutic drugs. Lipiodol has the unique property of selective uptake and retention in hyperarterialyzed liver tumors (15). Generally, two or three kinds of chemotherapeutic drugs (such as doxorubicin, epirubicin, idarubicin, mitomycin C, or cisplatin), are emulsified in the lipiodol, and then followed by particle embolization to improve the overall survival rate of patients with HCC (16). However, TACE inevitably leads to hypoxic damage to hepatoma cells and surrounding liver tissues. PES is thought to be the result of therapeutic cytotoxicity, tumor ischemia, and intrahepatic and extrahepatic inflammation (9). Studies has showed that PES was associated with a worse survival and a two-fold increased risk of death (7). PEF, a common symptom of PES, was defined as body temperature greater than 38℃ within 3 days after TACE with no evidence of infection (10). Although this fever is self-limiting, which may not be significantly related to the long-term survival rate of patients after TACE (10), and symptomatic interventions can be taken if necessary to achieve satisfactory relief (17), PEF often prolongs hospitalization and leads to unnecessary use of antibiotics.

The incidence of PEF reported in the literature ranged from 20–70% (10–12, 18). This variation was likely attributed to measurement bias derived from differences in the definitions used. Nevertheless, the pathogenesis of PEF is still unclear. Most studies believe that lipiodol-induced embolism may lead to ischemia, hypoxia and necrosis of some normal hepatocytes (10). In addition, TACE itself can lead to

inflammatory factors release (19), such stimuli can contribute to stress responses in the human body (10).

Recently, studies have found APRI and ALBI to be predictors of postoperative outcome for patients undergoing liver surgery (20). Hence, the ALBI grade and APRI were introduced in this study to manifest or indicate the hepatic function as well as liver fibrosis and cirrhosis (14).Analysis of 252 patients in this study showed that the incidence of PEF was 17.5%, which was similar to most of previous studies (10, 12). Jun et al. retrospectively analyzed 443 HCC patients who underwent the first session of TACE and found that PEF developed in 117 patients (26.41%). A multivariate analysis using logistic regression showed that ALT value after TACE and the lipiodol dose ≥ 7 mL were independent predictive factors of PEF (10). Shim et al. found that pre-procedure serum bilirubin, ascites, tumor size and female gender predicted PEF in a cohort without background infective hepatitis patient (12). However, more previous study disclosed that a dosage of doxorubicin plus iodized oil > 23 mL during chemoembolization and tumor size > 3 cm were significant predictors associated with the development of PEF (18).

We found the occurrence of PEF was closely related to some clinical and laboratory variables. Among which, lopiodol emulsion dose, number of hepatoprotectants, K^+, and ALBI grade were independent risk factors for PEF. The results of cut-off value indicated that when lopiodol emulsion dose was greater than 6.5 mL, K^+ was greater than 4.25 mmol/L, ALBI grade was more than 1.5, special attention should be paid to the occurrence of PEF in these patients, and good monitoring and prevention should be done. Besides that, our limited data also indicated that the number of hepatoprotectants might be a protect factor for occurrence of PEF. In additon, the area under the ROC curve of validation cohort was 0.874, which indicated comparative stability and discriminative ability of this predictive model.

Here, we performed a single center, retrospective study and the race were limited to Asian, while it is necessary to validate a predict model against external centers with different geography and races. Second, most of our patients were accompanied with infection of HBV and liver cirrhosis which was in accordance with the background of high HBV prevalence rate in China. Detection and controlling for population stratification in association studies of hepatitis patients are needed in the following researches. Third, we did not consider the tumor size's influence on the PEF for patients' variant situation for surgical or disease progression. In consideration of situation of hepatoprotectants wide use in China, we added the number of hepatoprotectants in the analysis and found it maybe a potential protect factor for PEF. Further, how the hepatoprotectants actually act in PEF still need further well-designed study.

Conclusion

PEF is a common complication in patients with advanced, unresectable HCC. we found that lopiodol emulsion dose, number of hepatoprotectants, K^+, and ALBI grade are strong predictors for PEF. Moving forward, the multivariate logistic model of these factors shows a discriminative ability to predict PEF in the validation cohort.

Declarations

1. Ethics approval and consent to participate

For this type of study formal consent is not required. This article is compliance with Ethical Standards.

2. Consent for publication

Not applicable.

3. Availability of data and materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4. Competing interests

The authors declare that they have no competing interests.

5. Funding

This study was not supported by any funding.

6. Authors' contributions

D.T. and X.L. designed research. D.T. collected and analyzed the patient data. Q.L. and X.L. reviewed and revised the manuscript. All authors read and approved the final manuscript.

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.
2. Ginzberg D, Wong RJ, Gish R. Global HBV burden: guesstimates and facts. Hepatol Int. 2018;12(4):315–29.
3. Fan JH, Wang JB, Jiang Y, Xiang W, Liang H, Wei WQ, et al. Attributable causes of liver cancer mortality and incidence in china. Asian Pac J Cancer Prev. 2013;14(12):7251–6.
4. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–70.
5. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. J Clin Oncol. 2007;25(8):978–86.
6. European Association For The Study Of The. European Organisation For L, Treatment Of R. C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol.

2012;56(4):908–43.

7. Mason MC, Massarweh NN, Salami A, Sultenfuss MA, Anaya DA. Post-embolization syndrome as an early predictor of overall survival after transarterial chemoembolization for hepatocellular carcinoma. HPB (Oxford). 2015;17(12):1137–44.
8. Yang H, Seon J, Sung PS, Oh JS, Lee HL, Jang B, et al. Dexamethasone Prophylaxis to Alleviate Postembolization Syndrome after Transarterial Chemoembolization for Hepatocellular Carcinoma: A Randomized, Double-Blinded, Placebo-Controlled Study. J Vasc Interv Radiol. 2017;28(11):1503-11 e2.
9. Dhand S, Gupta R. Hepatic transcatheter arterial chemoembolization complicated by postembolization syndrome. Semin Intervent Radiol. 2011;28(2):207–11.
10. Jun CH, Ki HS, Lee HK, Park KJ, Park SY, Cho SB, et al. Clinical significance and risk factors of postembolization fever in patients with hepatocellular carcinoma. World J Gastroenterol. 2013;19(2):284–9.
11. Siriwardana RC, Niriella MA, Dassanayake AS, Liyanage CA, Upasena A, Sirigampala C, et al. Factors affecting post-embolization fever and liver failure after trans-arterial chemo-embolization in a cohort without background infective hepatitis- a prospective analysis. BMC Gastroenterol. 2015;15:96.
12. Shim JH, Park JW, Choi JI, Kim HB, Lee WJ, Kim CM. Does postembolization fever after chemoembolization have prognostic significance for survival in patients with unresectable hepatocellular carcinoma? J Vasc Interv Radiol. 2009;20(2):209–16.
13. Hiraoka A, Kumada T, Kudo M, Hirooka M, Tsuji K, Itobayashi E, et al. Albumin-Bilirubin (ALBI) Grade as Part of the Evidence-Based Clinical Practice Guideline for HCC of the Japan Society of Hepatology: A Comparison with the Liver Damage and Child-Pugh Classifications. Liver Cancer. 2017;6(3):204–15.
14. Ji F, Liang Y, Fu SJ, Guo ZY, Shu M, Shen SL, et al. A novel and accurate predictor of survival for patients with hepatocellular carcinoma after surgical resection: the neutrophil to lymphocyte ratio (NLR) combined with the aspartate aminotransferase/platelet count ratio index (APRI). BMC Cancer. 2016;16:137.
15. de Baere T, Arai Y, Lencioni R, Geschwind JF, Rilling W, Salem R, et al. Treatment of Liver Tumors with Lipiodol TACE: Technical Recommendations from Experts Opinion. Cardiovasc Intervent Radiol. 2016;39(3):334–43.
16. Takayasu K, Arii S, Ikai I, Kudo M, Matsuyama Y, Kojiro M, et al. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. AJR Am J Roentgenol. 2010;194(3):830–7.
17. Chung JW, Park JH, Han JK, Choi BI, Han MC, Lee HS, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. Radiology. 1996;198(1):33–40.
18. Li CP, Chao Y, Chen LT, Lee RC, Lee WP, Yuan JN, et al. Fever after transcatheter arterial chemoembolization for hepatocellular carcinoma: incidence and risk factor analysis. Scand J Gastroenterol. 2008;43(8):992–9.

19. Loosen SH, Schulze-Hagen M, Leyh C, Benz F, Vucur M, Kuhl C, et al. IL-6 and IL-8 Serum Levels Predict Tumor Response and Overall Survival after TACE for Primary and Secondary Hepatic Malignancies. Int J Mol Sci. 2018;19(6).
20. Zou H, Wen Y, Yuan K, Miao XY, Xiong L, Liu KJ. Combining albumin-bilirubin score with future liver remnant predicts post-hepatectomy liver failure in HBV-associated HCC patients. Liver Int. 2018;38(3):494–502.

Figures

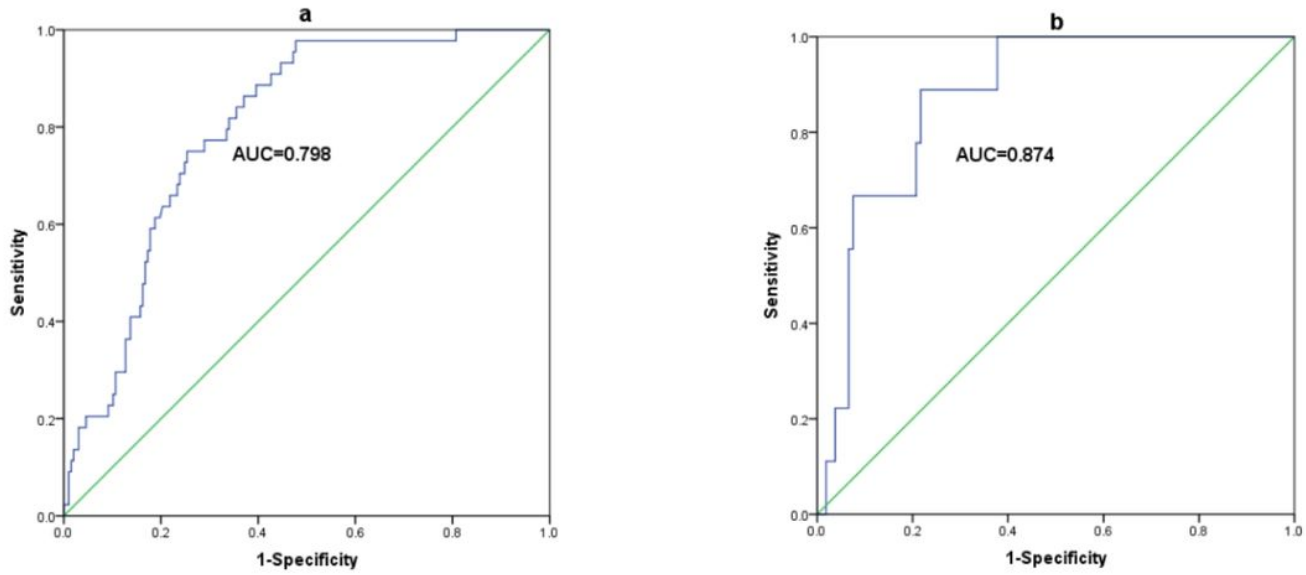

Figure 1

ROC curves determining model performance for prediction of PEF in a derivation cohort (n=252) and b validation cohort (n=115)