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Development of predisposition, injury, response, organ failure model for predicting acute kidney injury in acute on chronic liver failure

Rakhi Maiwall[1] | Shiv Kumar Sarin[1] | Suman Kumar[2] | Priyanka Jain[3] | Guresh Kumar[3] | Ajeet Singh Bhadoria[3] | Richard Moreau[4,5] | Chandan Kumar Kedarisetty[1] | Zaigham Abbas[6] | Deepak Amarapurkar[7] | Ankit Bhardwaj[3] | Chhagan Bihari[8] | Amna Subhan Butt[9] | Albert Chan[10] | Yogesh Kumar Chawla[11] | Ashok Chowdhury[1] | RadhaKrishan Dhiman[11] | Abdul Kadir Dokmeci[12] | Hasmik Ghazinyan[13] | Saeed Sadiq Hamid[9] | Dong Joon Kim[14] | Piyawat Komolmit[15] | George K. Lau[16] | Guan Huei LEE[17] | Laurentius A. Lesmana[18] | Kapil Jamwal[1] | Mamun-Al-Mahtab[19] | Rajendra Prasad Mathur[20] | Suman Lata Nayak[20] | Qin Ning[21] | Viniyendra Pamecha[22] | Diana Alcantara-Payawal[23] | Archana Rastogi[8] | Salimur Rahman[19] | Mohamed Rela[24] | Vivek A. Saraswat[25] | Samir Shah[26] | Gamal Shiha[27] | Barjesh Chander Sharma[28] | Manoj Kumar Sharma[1] | Kapil Sharma[1] | Soek Siam Tan[29] | Shivendra Singh Chandel[1] | Chitranshu Vashishtha[1] | Zeeshan A. Wani[1] | Man-Fung Yuen[30] | Osamu Yokosuka[31] | Ajay Duseja[11] | Wasim Jafri[9] | Harshad Devarbhavi[32] | C. E. Eapen[33] | Ashish Goel[34] | Ajit Sood[35] | Jia Ji[36] | Z. Duan[37] | Y. Chen[38] | of the APASL ACLF Research Consortium (AARC) working party

[1]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

[2]Department of Clinical Hematology, Command Hospital [Eastern Command], Kolkata, India

[3]Department of Clinical Research, Institute of Liver and Biliary Sciences, New Delhi, India

[4]UMR_S1149, Center for Research in Inflammation (CRI), Inserm and Paris Diderot University, Paris, France

[5]DHU Unity, Liver unit, Beaujon hospital, APHP, Clichy, France

[6]Department of Gastroenterology, Ziauddin University Hospital, Karachi, Pakistan

[7]Department of Gastroenterology and Hepatology, Bombay Hospital and Medical Research, Mumbai, India

[8]Department of Pathology, Institute of Liver and Biliary Sciences, New Delhi, India

[9]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

[10]Department of Surgery, Division of Hepatobiliary and Pancreatic surgery, and Liver Transplantation, The University of Hong Kong, Hong Kong, China

[11]Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

[12]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey

[13]Department of Hepatology, Nork Clinical Hospital of Infectious Diseases, Yerevan, Armenia

Abbreviations: AARC, APASL ACLF Research Consortium; ACLF, Acute on Chronic Liver Failure; AKI, Acute Kidney Injury; APASL, Asian Pacific Association for the Study of the Liver; ATN, Acute tubular necrosis; AUC, Area under ROC; CI, Confidence Interval; C-Index, Concordance Index; CLD, Chronic Liver Disease; CLIF-C ACLF Score, CLIF-Consortium ACLF Score; CLIF-SOFA, Chronic Liver Failure-Sepsis Organ Failure Assessment score; CTP, Child-Turcott Pugh; EASL-CLIF, European Association for Study of Liver-Chronic Liver Failure Consortium; HCC, Hepatocellular carcinoma; HE, Hepatic encephalopathy; HRS, Hepatorenal Syndrome; I-ACLF, Infection related ACLF; INR, International normalized ratio; KF, Kidney Failure; MAP, Mean Arterial Pressure; MELD, Model for End Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; PIRO, Predisposition, infection/inflammation, response, organ failure; RRT, Renal Replacement therapy; SBP, Spontaneous bacterial peritonitis.

[14]Center for Liver and Digestive Diseases, Hallym University Chuncheon Sacred Heart Hospital, Gangwon-Do, Korea
[15]Department of Medicine, Division of Gastroenterology and Hepatology, Chulalongkorn University, Bangkok, Thailand
[16]Department of Hepatology, The Institute of Translational Hepatology, Beijing 302 Hospital, Beijing, China
[17]Department of Medicine, National University Health System, Singapore, Singapore
[18]Division of Hepatology, University of Indonesia, Jakarta, Indonesia
[19]Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[20]Department of Nephrology, Institute of Liver and Biliary Sciences, New Delhi, India
[21]Department of Infectious Disease, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[22]Department of Hepatobiliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India
[23]Department of Hepatology, Cardinal Santos Medical Center, Manila, Philippines
[24]Institute of Liver diseases and Transplantation, Global Health city, Chennai, India
[25]Department of Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India
[26]Department of Hepatology, Global Hospitals, Mumbai, India
[27]Department of Internal Medicine, Egyptian Liver Research Institute and Hospital, Cairo, Egypt
[28]Department of Gastroenterology, GB Pant Hospital, New Delhi, India
[29]Department of Hepatology Selayang Hospital, Selangor, Malaysia
[30]Department of Medicine, The University of Hong Kong, Hong Kong, China
[31]Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Chiba, Japan
[32]Department of Gastroenterology, St.John's Medical College and Hospital, Bangalore, India
[33]Department of Gastroenterology and Hepatology, CMC, Vellore, India
[34]Department of Gastroenterology, Rome, NY, USA
[35]Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India
[36]Department of Gastroenterology, Liver Research Center, Beijing, China
[37]Department of Gastroenterology, Nanjing First Hospital, Nanjing, China
[38]Department of Gastroenterology, East Brunswick, NJ, USA

Correspondence
Dr. Shiv Kumar Sarin, MD, DM, FNA, FNASc, Professor and Head, Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India.
Email: shivsarin@gmail.com

Handling Editor: Dominique Thabut

Abstract

Background and Aim: There is limited data on predictors of acute kidney injury in acute on chronic liver failure. We developed a PIRO model (Predisposition, Injury, Response, Organ failure) for predicting acute kidney injury in a multicentric cohort of acute on chronic liver failure patients.

Patients and Methods: Data of 2360 patients from APASL-ACLF Research Consortium (AARC) was analysed. Multivariate logistic regression model (PIRO score) was developed from a derivation cohort (n=1363) which was validated in another prospective multicentric cohort of acute on chronic liver failure patients (n=997).

Results: Factors significant for P component were serum creatinine[(≥2 mg/dL)OR 4.52, 95% CI (3.67-5.30)], bilirubin [(<12 mg/dL,OR 1) vs (12-30 mg/dL,OR 1.45, 95% 1.1-2.63) vs (≥30 mg/dL,OR 2.6, 95% CI 1.3-5.2)], serum potassium [(<3 mmol/LOR-1) vs (3-4.9 mmol/L,OR 2.7, 95% CI 1.05-1.97) vs (≥5 mmol/L,OR 4.34, 95% CI 1.67-11.3)] and blood urea (OR 3.73, 95% CI 2.5-5.5); for I component nephrotoxic medications (OR-9.86, 95% CI 3.2-30.8); for R component,Systemic Inflammatory Response Syndrome,(OR-2.14, 95% CI 1.4-3.3); for O component, Circulatory failure (OR-3.5, 95% CI 2.2-5.5). The PIRO score predicted acute kidney injury with C-index of 0.95 and 0.96 in the derivation and validation cohort. The increasing PIRO score was also associated with mortality (P<.001) in both the derivation and validation cohorts.

Conclusions: The PIRO model identifies and stratifies acute on chronic liver failure patients at risk of developing acute kidney injury. It reliably predicts mortality in these patients, underscoring the prognostic significance of acute kidney injury in patients with acute on chronic liver failure.

KEYWORDS

acute kidney injury, acute on chronic liver failure, liver failure, Multiple organ failure, PIRO

1 | INTRODUCTION

Acute on chronic liver failure (ACLF) is a distinct syndrome which is characterized by an acute insult on a background of chronic liver disease. The unique feature of this syndrome is a high potential of reversibility.[1] Emergency liver transplant remains the only feasible therapeutic option, however, is not possible in some patients because of the presence of extrahepatic organ failures which contraindicate transplant. Currently, ACLF is defined by two different definitions in two different parts of the world. The Asia Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) consensus defined ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin≥5 mg/dL) and coagulopathy (INR≥1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[1] While recently, the EASL-Chronic Liver Failure Consortium (EASL-CLIF) proposed new diagnostic criteria for ACLF based on analyses of patients with cirrhosis and organ failure.[2] There are definite areas of uncertainty in defining patients with ACLF and therefore the exact pathogenesis remains an enigma and still remains to be elucidated. However, despite all the ambiguity and heterogeneity in the definitions in alteration of host response to injury, infection coupled by unregulated inflammation play an important patho-physiological role for development of this syndrome.[3]

Kidney dysfunction has been known to be associated with an ominous prognosis in patients with ACLF and has been incorporated as a defining condition for ACLF according to the EASL-CLIF consortium.[2] Infact, presence of kidney failure defined as serum creatinine ≥2 mg/dL constitutes ACLF grade I according to this definition. In a recent multicentric prospective study from North American Consortium for the Study of End-Stage Liver Disease (NACSELD) database wherein survival analysis was done for cirrhotic patients hospitalized with an infection which was defined as infection related ACLF (I-ACLF), it was reported that the presence of two or more organ failures was predictive of poor survival and serum creatinine was an independent predictor of mortality.[4] Therefore, both studies from the East and the West clearly signify the prognostic implication of kidney dysfunction in patients with ACLF.

The predisposition, infection/inflammation, response, organ failure (PIRO) concept is used for sepsis to stratify patients with different outcomes.[5] The PIRO could also be useful in understanding the pathophysiology of kidney dysfunction in patients with ACLF. However, currently, there are no predictive models for AKI in patients with ACLF.[6] We therefore aimed to develop a simple and concept based PIRO model to identify variables for predicting AKI in patients with ACLF. Second, we aimed to validate the model both internally by bootstrapping and externally in another multicentric prospective cohort of patients with ACLF.

Keypoints

- Kidney dysfunction or failure is known to have an ominous prognosis in patients with ACLF, however, currently there are no predictive models available for AKI in ACLF.
- The predisposition, infection/inflammation, response, organ failure (PIRO) can be used to identify pathophysiology and predictors of AKI in ACLF.
- First large multicentric multinational cohort study which identifies predictors of AKI in ACLF using the novel PIRO concept.
- PIRO model identifies and stratifies ACLF patients at risk of AKI with an excellent accuracy.

2 | PATIENTS AND METHODS

For the derivation cohort, retrospective-prospectively collected multicentric data from 17 university hospitals across the Asia Pacific from October 2012 to December 2013 was retrieved using the AARC database and analysed. The database includes data from all the participating centres to identify patients with ACLF according to the APASL ACLF 2009 definition (Table S1). The validation cohort comprised of a prospective cohort of 997patients from the AARC database from December 2013-January 2016. The diagnosis of cirrhosis was based on a composite of clinical signs and findings provided by laboratory test results, endoscopy, and radiological imaging or liver biopsy findings if available. The monitoring and management of patients was as per the standard of care. An informed written consent was taken from each patient at the time of enrolment. Ethical approval was obtained from Institutional ethics committee of Institute of Liver and Biliary Sciences, New Delhi, India.

2.1 | Inclusion criteria

Adult patients (aged>18 years) with ACLF defined according to APASL consensus ie as an acute hepatic insult manifesting as

jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR≥1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease were included in this study for development of PIRO model for AKI at day 7. For all included patients, the admission serum creatinine was considered as baseline which was used for defining the development of AKI at day 7. Acute kidney injury was defined as an increase of serum creatinine of more than 0.3 mg/dL within 48 hours or 50% increase from the admission value at day 7 and/or requirement of renal replacement therapy.[7] Patients with a clear diagnosis of acute liver failure, HCC and extrahepatic malignancies, obstructive uropathy, and those who underwent liver transplant were also excluded from this study.

2.2 | Building of the prediction model PIRO

The data were collected including all the variables defined according to each PIRO component as follows (detail definitions in Appendix S1):

2.2.1 | Predisposition

Patient demographics (age and gender), etiology of underlying chronic liver disease, presence and severity of ascites, comorbidities including chronic kidney disease,[8] coronary artery disease based on angiography or echocardiography, hypertension, and diabetes mellitus. All available baseline biochemical parameters ie serum haemoglobin, leucocyte and platelet counts, serum sodium, potassium, urea, creatinine, bilirubin, INR, albumin, were considered for evaluation of significant factors for predisposition of AKI.

2.2.2 | Injury

For injury, the following variables were considered ie diuretic use, nephrotoxic medication use,[9]bacterial infections,[10] variceal bleed[11] and etiology of acute insult at baseline.

2.2.3 | Response

Included presence of systemic inflammatory response syndrome.[10]

2.2.4 | Organ failure

Included extrahepatic organ failures except renal failure defined as circulatory failure; cerebral failure; and respiratory failure.[2]

2.3 | Statistical methods

2.3.1 | Analyses of baseline characteristics

Baseline characteristics were summarised with median (and interquartile range) for continuous data and proportions for categorical data. Comparison of the variables across groups (derivation and validation) were done by Chi-Square test for categorical data, Mann–Whitney for non-parametric or Students *T* test for parametric continuous variables respectively. Ninety-five percent confidence intervals were reported and equivalent value of 0.05 was used for tests of significance.

TABLE 1 Baseline Characteristics of the study cohort

Variable	Derivation Cohort (n=1363)	Validation Cohort (n=997)	*P*
Age[b]	44.3 (12.9)	44.1 (12.3)	0.85
Gender-Male	1129 (83)	817 (82%)	0.58
Comorbidity	558 (41)	418 (42%)	0.63
Fever	283 (21)	211 (23.6)	0.12
Alcohol as etiology of chronic liver disease	645 (47.3)	487 (48.9)	0.48
Alcohol as acute insult	563 (41.3)	433 (43.4)	0.30
Ascites (Present)	961 (70.5)	770 (72.3)	0.33
SIRS	534 (46.8)	432 (43.4)	0.11
Variceal Bleed	133 (9.8)	105 (12.1)	0.08
Bacterial Infections	383 (28.1)	226 (26.3)	0.33
Haemoglobin (g/dL)[b]	10.8 (2.6)	10.5 (2.15)	0.001*
Platelet count ($\times 10^9$cells/L)[a]	135 (2-670)	140 (15-670)	0.45
TLC 10^9 cells/L)[a]	11.1 (0.12-62)	12.8 (1.8-61.7)	<0.001
Urea (mg/dL)[a]	41 (23-83)	36 (21.4-72)	0.66
Serum creatinine (mg/dL)[a]	1.03 (0.63-1.8)	0.9 (0.6-1.82)	0.51
Sodium (mEq/L)[b]	131.8 (8.9)	130.7 (8.17)	0.003*
Potassium (mEq/L)[a]	3.8 (3.2-4.5)	3.86 (3.3-4.5)	0.41
Total bilirubin (mg/dL)[a]	19 (5-55.56)	21.5 (5-56.5)	<0.001
Albumin (g/dL)[b]	2.3 (0.68)	2.1 (0.59)	<00.001*
INR[a]	2.3 (1.9-3)	2.12 (1.75-2.8)	0.82
CTP[b]	11.2 (1.98)	10.8 (1.48)	<0.001*
MELD[b]	30.24 (8.4)	30.4 (7.97)	0.65
CLIF-SOFA[b]	13.1 (2.67)	11.7 (1.85)	<0.001
CLIF-C ACLF[b]	101.18 (11.2)	96.07 (8.49)	<0.001

CLIF-C ACLF Score, CLIF-Consortium ACLF Score; CLIF-SOFA, Chronic Liver Failure-Sepsis Organ Failure Assessment score; CTP, Child-Turcott Pugh; INR, International Normalized Ratio; MELD, Model for End Stage Liver Disease; TLC, Total Leucocyte counts.

Data presented as median (interquartile range)[a] or mean(standard deviation)[b.]

Quantitative data presented as number(percentage).

*The differences are not clinically significant, however, *P* values are significant because of very large sample-size.

2.3.2 | Primary outcome

Primary outcome was development of acute kidney injury at day 7.

2.3.3 | Secondary outcome

Death because of any reason.

2.3.4 | Variables for PIRO

Initially variables were selected for each of the components of PIRO as defined in the methods. All these variables were measured at enrolment. They were compared amongst patients who developed AKI and those who did not develop using univariate logistic regression analysis. Variables significant (P<.05) on univariate analysis were considered for multivariate analysis. The C-index (AUROC) of each variable was also calculated.

2.3.5 | Development of model

Initially logistic regression model was fitted for all the variables (including provision for non-linearity). Multivariate logistic regression analysis was done using backward elimination procedure for selection of final variables for the PIRO model. The score was computed using the coefficients of the final variables in the PIRO. The calibration of the PIRO was assessed by comparing the actual observed risk and the average probability of developing AKI in the original data by graphical methods. The Hosmer-Lemeshow was used to assess the goodness-of-fit. The Harrell's concordance index (C-index) was used to assess the discriminatory ability of the model. Furthermore, a statistical comparison

TABLE 2 Univariate association of factors for each of the components of PIRO in the derivation cohort (n=1363)

Factors	AKI Absent (n=942)	AKI Present (n=421)	Crude Odd's Ratio, 95% Confidence Intervals	AUROC	*P*
Predisposition					
Age (Years)	44 (35-53)	45 (38-54)	1.02, 1.006-1.024	0.55	<.001
Gender (M:F)	753 (80%)	376 (89%)	2.09, 1.5-3	0.55	<.001
Presence of any Comorbidity	515 (54.7%)	278 (66.1%)	1.62, 1.01-2.01	0.53	.03
Etiology (Chronic) (Alcohol vs others)	480 (51)	261 (62)	1.5, 0.98-2.3	0.54	.06
Presence of Ascites	827 (88%)	377 (90%)	1.19, 0.83-1.74	0.51	.35
Haemoglobin (gm/dL)	11 (9-13)	10 (8-12)	0.86, 0.83-0.91	0.61	<.001
Leucocyte counts ($\times 10^9$ cells/L)	10 (7-14)	16 (11-22)	1.0, 1.000-1.001	0.71	<.001
Platelets ($\times 10^9$ cells/L)	140 (92-200)	124 (89-182)	1.0, 1.000-1.001	0.55	.012
Serum sodium (mEq/L)	133 (129-137)	130 (123-136)	0.97, 0.95-0.98	0.59	<.001
Serum potassium (mEq/L)	4 (3-4.3)	4 (4-5.1)	1.74, 1.56-1.94	0.66	<.001
Serum Urea (mg/dL)	25.2 (13-40.5)	97.5 (65-153)	1.05, 1.04-1.06	0.91	<.001
Serum Creatinine (mg/dL)	0.8 (0.55-1.1)	2.53 (1.88-3.9)	28.6, 19.6-43.3	0.93	<.001
Total Bilirubin (mg/dL)	18 (10-26)	24 (15-31)	1.05, 1.03-1.06	0.64	<.001
INR	2.02 (1.7-2.7)	2.44 (1.91-3.3)	1.14, 1.07-1.22	0.63	<.001
Serum albumin (g/dL)	2.4 (2-2.8)	2.2 (1.8-2.7)	0.79, 0.69-0.89	0.56	<.001
Injury					
Diuretic use	22 (2%)	28 (7%)	2.97, 1.7-5.3	0.52	<.001
Variceal Bleed	133 (14.2%)	55 (13.1%)	0.91, 0.87-1.21	0.51	.34
Nephrotoxicity	6 (1%)	25 (6%)	9.75, 4.2-26.7	0.93	<.001
Bacterial Infections	135 (24%)	45 (43%)	2.40, 1.56-3.7	0.60	<.001
Etiology (Acute insult)					
(Alcohol vs others)	410 (44%)	259 (62%)	2.07, 1.6-2.6	0.59	<.001
Response					
SIRS	361 (38%)	249 (59%)	2.3, 1.84-2.9	0.60	<.001
Organ Failure					
Circulatory failure	164 (17%)	198 (47%)	4.2, 3.3-5.4	0.65	<.001
Respiratory failure	309 (33%)	247 (59%)	2.91, 2.29-3.7	0.63	<.001
Cerebral failure	335 (36%)	272 (65%)	3.31, 2.6-4.2	0.65	<.001

TABLE 3 Multivariate Logistic regression analysis for the final PIRO model

Predisposition	Crude Odd's ratio	95% Confidence Intervals	*P*	Adjusted Odd's Ratio	95% Confidence Interval
S. Creatinine (mg/dL) ≥2	28.6	19.6-43.3	<.001	4.52	3.67-5.30
Serum Potassium (mEq/L)					
<3	1		.001	1	
3-4.9	2.6	1.6-4.2		2.7	1.05-1.97
≥5	8.6	8.6 (6.2-14.3)		4.34	1.67-11.3
Serum Bilirubin (gm/dL)					
<12	1		.03	1	
12-30	1.5	1.09-1.99		1.45	1.1-2.63
≥30	3.1	2.2-4.4		2.6	1.3-5.2
Serum Urea (mg/dL)	1.05	1.04-1.06	<.001	3.73	2.5-5.5
Injury					
Nephrotoxic drugs	9.75	4.2-26.7	<.001	9.86	3.2-30.8
Response					
Systemic Inflammatory Response Syndrome	2.3	1.8-2.9	.003	2.14	1.4-3.3
Organ Failure					
Circulatory Failure	4.2	3.3-5.4	<.0001	3.5	2.2-5.5

Components	Concordance Index 95% Confidence intervals	Calibration (Mean Absolute Error)	Sensitivity	Specificity	Nagelkerke R square
P	0.938 (0.922-0.954)	0.02	76.4%	98.4%	0.75
P+I	0.943 (0.928-0.959)	0.014	78%	98.1%	0.76
P+I+R	0.949 (0.936-0.963)	0.008	80%	98.0%	0.77
P+I+R+O	0.954 (0.941-0.967)	0.006	80.5%	98.0%	0.78

"I"-Injury, "O"-Organ Failure, "P"- Predisposition, "R"- Response.

of the C-index of the PIRO score with the MELD, MELDNa, CTP, CLIF-SOFA and CLIF-C ACLF scores we used the integrated discriminating improvement statistic. For external validation, similarly PIRO score was computed from the validation data and score performance assessed and compared by using the same methods as for the original derivation data.

Finally, a nomogram, scoring system and online calculator was developed for usage in clinical practice. Data were analysed using SPSS, version 18 for Windows (Chicago, IL) and R version 3.2.1 (R Core Team [2014]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.)

3 | RESULTS

Of the 1363 patients of ACLF studied, 1129 (83%) were males with a mean age of 44 (SD 12.9) years. Five-hundred and twenty-seven (39%) patients died at a follow-up of 62 days median (IQR 21-301 days). AKI at day 7 developed in 421 (31%) patients. The median (IQR) MELD, CLIF-SOFA, CLIF-C ACLF score were 29.7 (24.7-35.9), 13 (11-15) and 101.18 (92.77-107.84) respectively. The baseline characteristics of patients are depicted in Table 1.

3.1 | Development of PIRO model

3.1.1 | Predisposition

Age (p, OR, 95% CI) (<0.001,1.02, 1.006-1.024), gender (<0.001, 2.09, 1.5-3), serum creatinine (<0.001,28.6,19.6-43.3), urea (<0.001,1.05, 1.04-1.06), serum potassium (<0.001,1.74,1.56-1.94), serum bilirubin (<0.001, 1.05,1.03-1.06), serum albumin (<0.001,0.79,0.69-0.89), INR (<0.001.1.14,1.07-1.22), haemoglobin (<0.001, 0.86,0.83-0.91), leucocyte (<0.001,1.0,1.000-1.001), platelet counts (0.012,1.0,1.000-1.0010 and serum sodium (<0.001, 0.97,0.95-0.98) were significant on univariate analysis (Tables 2 and 3).

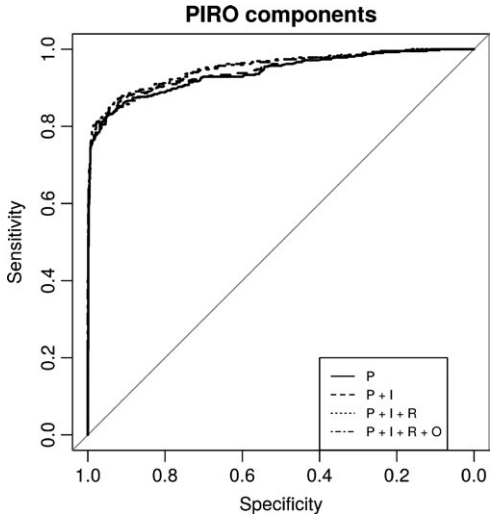

FIGURE 1 Area under the receiver operating curves (AUROC) of the individual components of PIRO (Predisposition, Predisposition+Injury, Predisposition+Injury+Response and Predisposition+Injury+Response+Organ Failure)

3.1.2 | Injury

Diuretics (p,OR,95% CI) (0.012, 2.97, 1.7-5.3), bacterial infections (<0.0001, 2.3, 1.5-3.7) and nephrotoxic medication use (<0.0001, 9.75, 4.2-26.7) as well as alcohol as an acute insult (<0.001, 2.1, 1.6-2.6) were significant on univariate analysis.

3.1.3 | Response

Presence of SIRS (0.02, 1.7, 1.07-2.84) significantly predicted development of AKI.

3.1.4 | Organ failure

Presence of each of the extrahepatic organ failures ie circulatory failure (<0.001, 4.2, 3.3-5.4), respiratory failure (<0.0001, 2.9, 2.29-3.7) and cerebral failure (<0.0001, 3.31, 2.6-4.2) were associated with development of AKI.

All significant factors on univariate analysis for each of the component of PIRO were considered for multivariate analysis by logistic regression to develop the final PIRO score. The significant factors identified for the "P" component were serum creatinine ([≥2 mg/dL] OR 4.52, 95% CI [3.67-5.30]), serum bilirubin ([<12, OR 1] vs [12-30, OR 1.45, 95% 1.1-2.63] vs [≥30, OR 2.6, 95% CI 1.3-5.2]), potassium ([<3 OR-1] vs [3-4.9, OR 2.7, 95% CI 1.05-1.97] vs [≥5, OR 4.34, 95% CI 1.67-11.3]) and serum urea (OR 3.73, 95% CI 2.5-5.5) (Fig. S1). The different cut-off's for serum creatinine and bilirubin were in accordance to the previously published criteria for defining kidney and liver failure by the Canonic study while these cut-offs were based on theoretical knowledge for serum potassium.[2] Nephrotoxic medication use for the "I" component (*P*<.001, OR 9.86, 95% CI 3.2-30.8), SIRS for the "R" component (*P*=.003, OR 2.14, 95% CI 1.4-3.3) and circulatory failure for the "O" component (*P*<.001, OR 3.5, 95% CI 2.2-5.5) were significant on multivariate analysis (Table 3).

There was an increase in the C-index even though not significant from 0.94 for "P" component to 0.95 after considering the addition of "I", "R" and "O" components (Figure 1). However, a significant improvement in model calibration and increase in model sensitivity was achieved by considering all components of the PIRO score. (Table 3, Figure 2, Table S1).

3.2 | Validation of the derived model PIRO

3.2.1 | Internal validation

The PIRO model was internally validated by bootstrapping in the derivation cohort. The C index was 0.949 (95% CI 0.936-0.962), and mean absolute error in calibration curve was 0.006 (Fig. S2).

3.2.2 | External validation

The model was also externally validated in a prospective multicentric cohort of patients with ACLF (n=997) from the AARC database. The validation cohort comprised of males 817 (82%) with a mean age of 44.1(12.3) years. The validation cohort showed some significant differences in parameters from the derivation cohort (Table 1). These differences even though not clinically relevant were statistically significant because of the extremely large sample size of the cohort. Despite this, the C-index of the model in the validation dataset was also 0.96 (95% CI: 0.94-0.97) and showed an excellent discrimination (Fig. S2).

3.3 | Comparison of PIRO with other Scores

We compared the performance of the developed PIRO score for prediction of AKI with the well-established scores ie the MELD, MELDNa, CTP, CLIF-SOFA and CLIF-C ACLF score. (Table 4). PIRO score had a C-index of 0.95 (95% CI: 0.94-0.96) in the derivation and 0.96 (95% CI: 0.94-0.97) in the validation cohort which was superior to MELD C-index 0.88 (0.86-0.90) and 0.92 (0.90-0.93), MELDNa 0.88 (0.87-0.90) and 0.92 (0.90-0.93), CTP 0.67 (0.65-0.70) and 0.61 (0.57-0.66), CLIF-SOFA 0.67 (0.63-0.71) and 0.82 (0.79-0.85) as well as the CLIF-C ACLF score 0.64 (0.60-0.68) and 0.82 (0.79-0.85) respectively (Figure 3A,B).

3.4 | PIRO model and mortality

It is well-known that development of AKI is associated with mortality in patients with cirrhosis. We therefore went on further to evaluate the association of the derived PIRO score also with mortality. For this we divided the linear predictors from the PIRO model into three quantiles and developed Kaplan–Meier survival curves for both the derivation (Figure 4A) and validation cohorts (Figure 4B) which showed a significant difference between the three different quantiles highlighting the prognostic significance of PIRO score for not only prediction of AKI but also mortality in patients with ACLF. The C-Index of PIRO for mortality was 0.73 and 0.82 in the derivation and validation cohorts respectively (Table S2 and Figure 2).

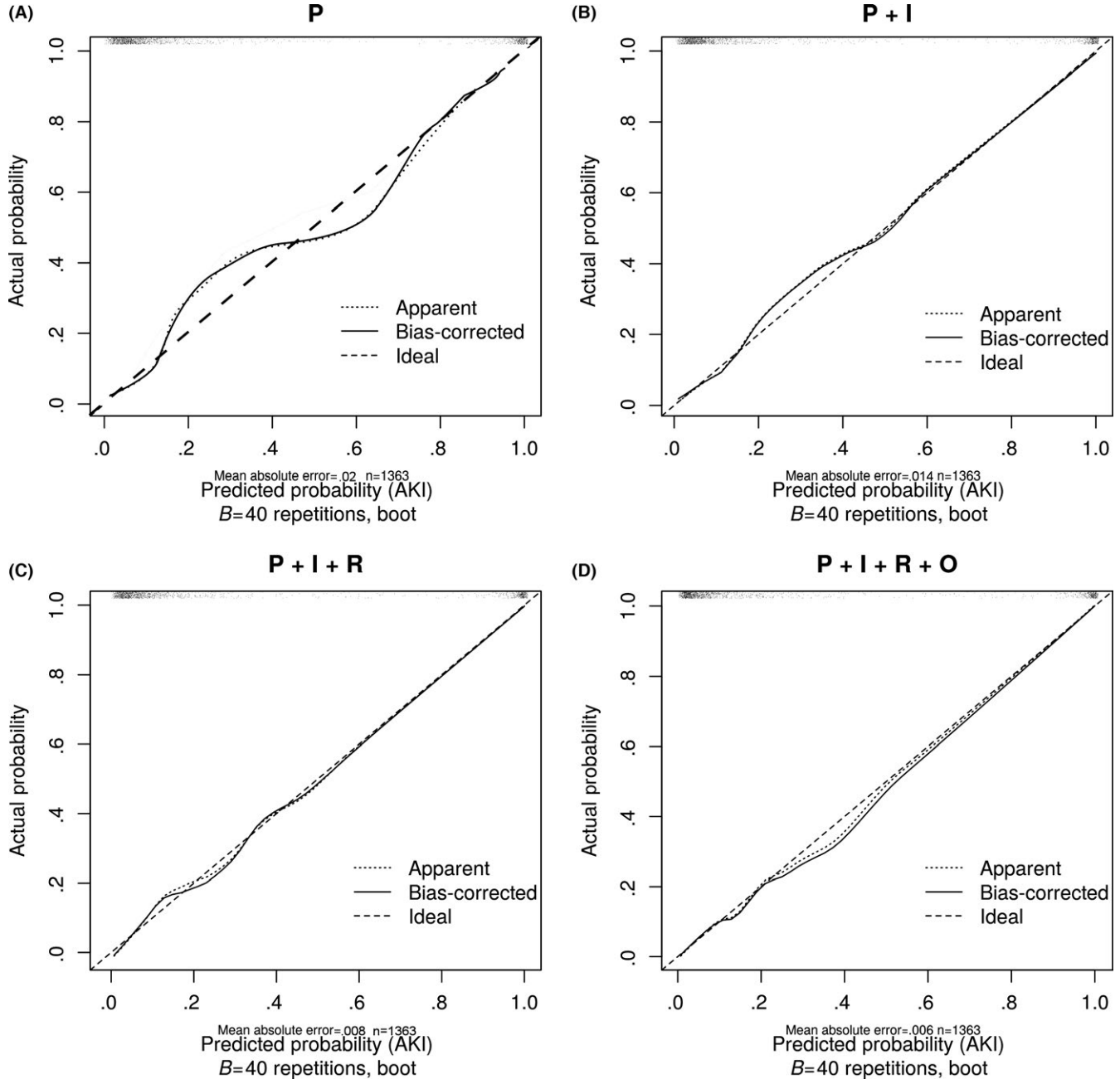

FIGURE 2 Calibration plot depicting individual components of the PIRO (A) Predisposition (B) Predisposition+Injury, (C) Predisposition+Injury+Response (D) Predisposition+Injury+Response+Organ Failure

3.5 | Presentation of Model

A predictive nomogram was also made to calculate the PIRO score for predicting the development of AKI (Fig. S3).

Online calculator for PIRO score to predict the risk of development of AKI in ACLF https://sumprain.shinyapps.io/ilbs_piro_calc.

4 | DISCUSSION

This is the first large multicentric and multinational cohort study based on AARC database, which has looked at predictors of acute kidney injury with the help of a simple and concept based PIRO model in patients with ACLF.[1]

Kidney dysfunction is a heterogeneous clinical syndrome which is contributed both by modifiable (*injury, response and organ failure component of PIRO*) and non-modifiable factors (*predisposition component of PIRO*).[12,13] Of all the available parameters which were considered for predisposition we found that a high baseline serum urea and creatinine, hyperkalemia, combined with hyperbilirubinemia as significant predictors for development of AKI. High bilirubin is an important parameter to signify the severity of liver failure in patients of ACLF.[1,2] and therefore pathophysiologically this shows a direct correlation of liver failure in determining AKI in these patients. Furthermore, high

TABLE 4 Comparison of PIRO with other prognostic scores for prediction of AKI

	Derivation Cohort (n=1363)		Validation Cohort (n=997)	
	C-Index, 95% Confidence Intervals	Somer's D	C-index 95% Confidence Interval	Somer's D
MELD	0.88 (0.86-0.90)	0.76	0.92 (0.90-0.93)	0.85
MELDNa	0.88 (0.87-0.90)	0.76	0.92 (0.90-0.93)	0.85
CTP	0.67 (0.65-0.70)	0.34	0.61 (0.57-0.66)	0.23
CLIF-SOFA	0.67 (0.63-0.71)	0.34	0.51 (0.46-0.55)	0.01
CLIF-C ACLF	0.64 (0.60-0.68)	0.28	0.82 (0.79-0.85)	0.64
PIRO	0.95 (0.94-0.96)	0.90	0.96 (0.94-0.97)	0.91

C-Index, Concordance Index; CLIF-C ACLF Score, CLIF-Consortium ACLF Score; CLIF-SOFA, Chronic Liver Failure-Sepsis Organ Failure Assessment score; CTP, Child-Turcott Pugh; MELD, Model for End Stage Liver Disease; MELDNa, Model for End Stage Liver Disease Sodium score; PIRO, Predisposition, Injury,Response and Organ Failure score; Somer's D.

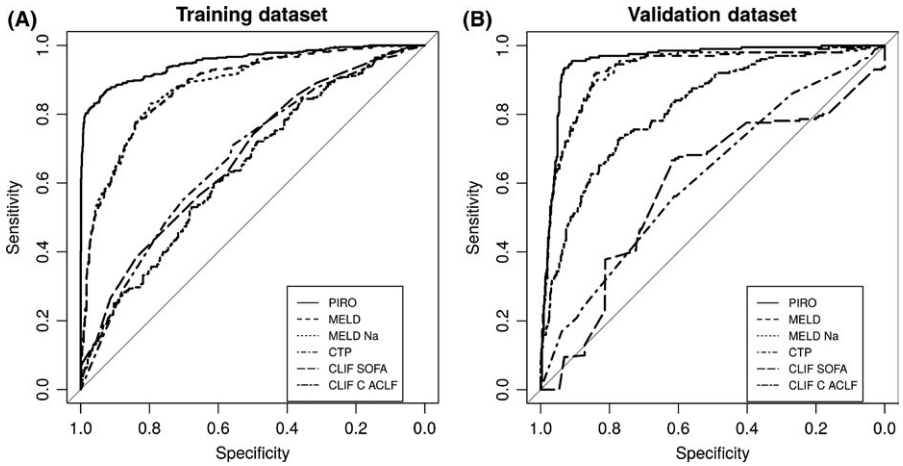

FIGURE 3 Comparison of PIRO with other scores (MELD, MELDNa, CTP, CLIF-SOFA, CLIF-C ACLF) (A) Derivation cohort and (B) Validation cohort

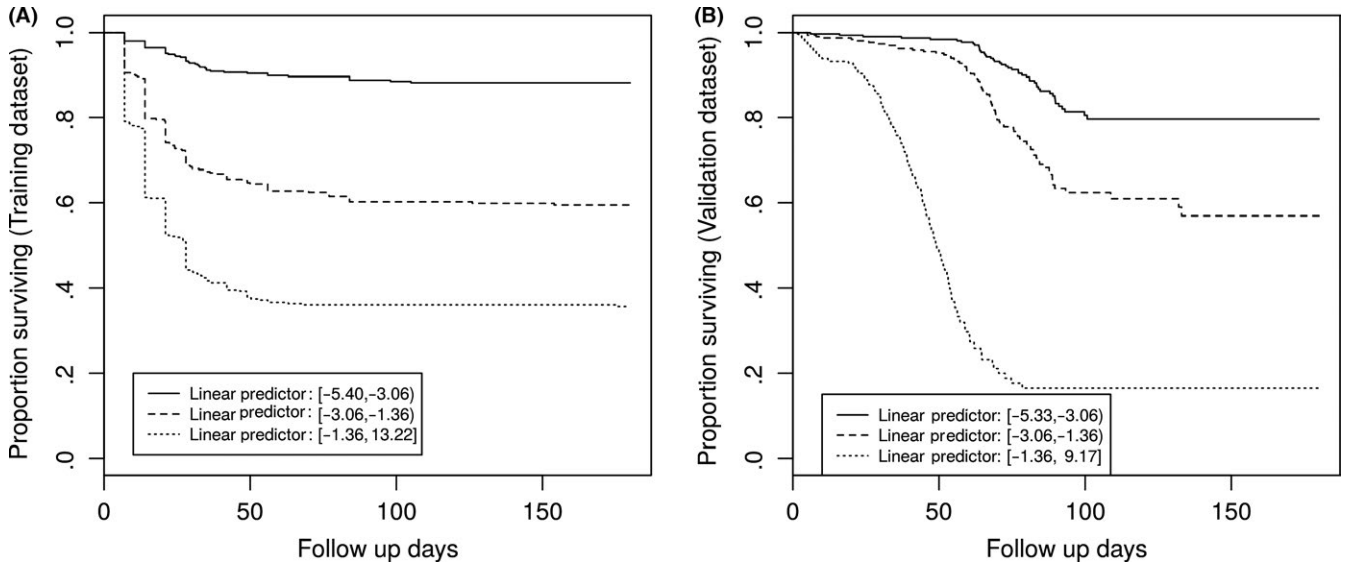

FIGURE 4 Kaplan–Meier Survival curves showing linear predictors from the PIRO score and their division into three quantiles (A) Derivation cohort and (B) Validation cohort

bilirubin can not only cause spuriously low serum creatinine but also can cause toxic damage to the tubules.[12] The predictive capability of hyperkalemia is well-evidenced by the fact that impaired potassium homeostasis in the body is predominantly governed by renal dysfunction.[14] Similarly, high urea and serum creatinine which are important determinants of renal dysfunction formed significant factors for the predisposition score. Interestingly, the cut-off's for bilirubin and serum creatinine in the PIRO score were consistent with the cut-off's proposed for defining liver failure and kidney failure by the investigators of the EASL-CLIF consortium.[2]

For the injury component, exposure to nephrotoxic medications was the only significant factor on multivariate analysis. Thus, in all patients with ACLF at baseline it becomes important to avoid injury by nephrotoxic agents specifically drugs like aminoglycoside antibiotics, intravenous contrast agents, angiotensin receptor antagonists or receptor blockers, non-steroidal anti-inflammatory drugs etc. which should therefore be used very judiciously considering their risk to potentiate kidney damage.

The third essential component of PIRO is constituted by the host's response to the injury or the development of systemic inflammatory response syndrome. This was investigated as the R component of PIRO in our study. Presence of SIRS shows the inherent susceptibility or a reduced tolerance of the kidneys to systemic inflammation in patients with ACLF. The association of systemic inflammation in the development of functional renal failure was initially shown by Thabut et al. and recently by us and Altamirano et al.[15–18] Presence and severity of inflammation has also been shown to predict a poor response to the vasoconstrictors in patients with HRS and liver failure.[19] In future, more studies are needed to study whether drugs to combat systemic inflammation would be helpful in preventing kidney dysfunction in all patients with ACLF with SIRS at baseline The pathophysiological relationship of systemic inflammation in the development of AKI has been demonstrated for the first time in a large cohort of patients with ACLF and therefore provides rationale to explore the mechanisms and management of this entity and see whether it has an impact on the evolution of kidney injury in these patients.

The influence of extra-hepatic organ failure on mortality has been well studied in patients with ACLF. It has been demonstrated that mortality is known to increase stepwise with the increase in the number of organ failures and is highest for patients with multi-organ failure ie sequential presence of two or more extra-hepatic organ failures. In our study, a strong association of AKI was seen with all other extra-hepatic organ failures and specifically circulatory failure. Early and aggressive management of circulatory shock is therefore very necessary for preventing damage to the kidneys in ACLF.

The PIRO score predicted AKI with a significant better accuracy than the well-established prognostic scores ie MELD, MELDNa, CTP, CLIF-SOFA and CLIF-C ACLF score. However, it is noteworthy to mention that none of these scores were developed for the prediction of AKI in patients with ACLF, and therefore it was not surprising for the PIRO score to be superior to these scores for prediction of AKI in both the derivation and validation cohorts. The PIRO score which was developed for predicting AKI also predicted mortality in these patients. The PIRO model includes the host status, the inciting event, the clinical and biochemical stage of the patient to finally predict the outcome. In-hospital AKI is already known to have a poor prognosis in patients with cirrhosis; however, this has not been studied for patients with ACLF. The results of our study provide a 'golden window' for therapeutic interventions to prevent AKI based on stratification of patients by the novel PIRO model. However, because we considered admission serum creatinine for diagnosing AKI, it is quite possible that many patients would have already developed renal dysfunction prior to presentation. Therefore, PIRO can identify and stratify patients at any stage of kidney dysfunction.

The major strength of our study remains the analysis of a large multicentric cohort of patients wherein all the data were entered on to a comprehensive electronic medical record system at the AARC database, even though a part of the data that was collected was retrospective. Our study, for the first time identifies predictors of AKI in patients with ACLF from a very large cohort of patients with ACLF and further the results were validated in another large multicentric cohort. The PIRO model was developed using AARC database for prediction of AKI, but also holds relevance for patients with ACLF defined according to the EASL-CLIF consortium wherein kidney dysfunction or failure constitutes a defining condition for ACLF. Furthermore, the cut-off for serum bilirubin and serum creatinine in the PIRO score are consistent with the cut-off proposed for liver and kidney failure by the EASL-CLIF validating the prognostic utility of these cut-offs in patients with ACLF irrespective of AARC or CLIF definition. The developed PIRO model also helps in identifying the pathophysiological basis of kidney dysfunction in patients with ACLF. Incorporation of biomarkers (for instance urine NGAL) in the P-score could further help in differentiating functional from structural kidney damage. Furthermore, to maximize clinical use, the model has been made very simple with all factors which are easily available. The PIRO model is reliable and serves well to predict the prognosis in cirrhotic patients with AKI, and it was validated both internally as well as externally.

To summarize, the PIRO score derived and validated from a very large multicentric multinational cohort of ACLF patients predicts AKI with an excellent accuracy.

CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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