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Association Between Platelet-Albumin-Bilirubin Grade and the 30-Day Mortality in Patients with Acute Respiratory Distress Syndrome: Evidence from the MIMIC-IV Database

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Background: The platelet-albumin-bilirubin (PALBI) grade is a comprehensive assessment index of liver function. Liver dysfunction is a key determinant of the pathogenesis and resolution of acute respiratory distress syndrome (ARDS), which affects the prognosis of patients.

Aims: To evaluate the association of PALBI grade with the risk of 30-day mortality in patients with ARDS.

Study Design: Retrospective cohort study.

Methods: Univariate and multivariate Cox proportional hazards models were used to evaluate the association between PALBI grade and the 30-day mortality in patients with ARDS; results were described as hazard ratios (HRs) and 95% confidence intervals (CIs). This association was further assessed by subgroup analyses stratified based on age, sex, and complications.

Results: A total of 2,841 patients with ARDS were included, of whom, 703 (24.74%) died within 30 days. After adjusting all covariates, a higher PALBI grade was associated with higher odds of 30-day mortality (HR: 1.55, 95% CI: 1.05-2.29). High PALBI grade was related to higher odds of 30-day mortality in patients with ARDS aged ≥ 65 years (HR: 2.30, 95% CI: 1.06-5.01), males (HR: 2.10, 95% CI: 1.29-3.44), without sepsis (HR: 1.71, 95% CI: 1.11-2.64), without pneumonia (HR: 1.86, 95% CI: 1.19-2.91), and without any history of chronic obstructive pulmonary disease (HR: 1.93, 95% CI: 1.28-2.91).

Conclusion: The PALBI grade was positively associated with 30-day mortality in patients with ARDS. The present study provides a reference for risk stratification management of patients with ARDS to improve short-term prognosis.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a type of respiratory failure caused by various disorders resulting in fluid accumulation in the lungs and low oxygen levels in blood and is associated with high mortality.[1-4] Globally, approximately 3 million patients suffer from ARDS each year, accounting for 10% of intensive care unit (ICU) admissions, and causing up to 24-46% of in-hospital deaths.[5,6] Despite many advancements in medical treatment and critical illness management, ARDS morbidity and mortality remain high and has emerged as a significant public disease burden.[7,8] Identification of indicators closely associated with the risk of mortality is of the essence for the management and improvement of the prognosis of patients with ARDS.

Inflammation, nutritional status, and liver function have a major effect on the occurrence and development of ARDS and affect the outcome of patients.[9-12] Lower platelet counts have been proven to be related to death risk in patients with ARDS, which may be related to platelet-mediated inflammatory and immune responses.[12,13] Albumin is an acute-phase protein involved in the nutritional status and inflammation levels.[14] Hoeboer et al.[15] suggested that lower albumin levels were related to poor prognosis in patients with ARDS such as prolonged hospital stays and increased mortality. Total bilirubin is considered a liver dysfunction biomarker, and a study reported that higher total bilirubin levels were associated with all-cause mortality in patients with ARDS.[16] The platelet-albumin-bilirubin (PALBI) grade is a comprehensive assessment indictor widely employed to evaluate liver function and the health outcomes

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of hepatocellular carcinoma (HCC), and itis a superior indicator than platelet, albumin, or bilirubin levels alone.[17-20] High PALBI grade is related to poor overall survival in patients with pancreatic cancer,[21] HCC,[19,22] and cirrhosis.[23,24] However, the association between PALBI grade and mortality in patients with ARDS remains unclear.

Hence, this study aimed to evaluate the association between PALBI grade and the risk of 30-day mortality in patients with ARDS. We also examined the effect of age, sex, and comorbidities on this association.

MATERIALS AND METHODS

Study design

Medical Information Mart for Intensive Care (MIMIC)-IV database is an extensive, public database that stores hospital data of patients admitted to the tertiary academic medical center in Boston, Massachusetts. This database contains information about laboratory measurements, medications, vital signs, etc. All subject records in the MIMIC-IV database were fully de-identified, and the requirement for individual subject consent was deemed unnecessary by the institutional review board of the Beth Israel Deaconess Medical Center.

Study population

In this study, patients aged ≥ 18 years with a diagnosis of ARDS on ICU admission were initially included. ARDS was defined based on Berlin definition as following: patients have pressure of alveolar oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤ 300 and are treated with mechanical ventilation with the minimum positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O on the first day of ICU admission.[25] Moreover, patients were admitted to the ICU for > 24 h.

Patients with missing data on bilirubin levels, albumin levels, and platelet counts and those with missing survival information were excluded from this study.

Potential covariates

The present study included various covariates, including sociodemographic information [age, sex (female/male), and race (white, unknown, or others)], ICU type (medical ICU/surgical ICU, or others), complications [acute kidney injury (AKI) stage, renal failure, atrial fibrillation, severe liver disease, sepsis, pneumonia, chronic obstructive pulmonary disease (COPD), and metastatic cancer], vital signs [heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate], scoring systems [sequential organ failure assessment (SOFA) score, Glasgow Coma Scale (GCS) score and Charlson Comorbidity Index (CCI)], important laboratory parameters [white blood cell (WBC), hemoglobin, red blood cell distribution width (RDW), hematocrit, blood urea nitrogen (BUN), glucose, bicarbonate, sodium, potassium, chloride, and international normalized ratio (INR)], blood gas analysis [pondus hydrogenii (pH), oxygen saturation (SpO_2), pressure of alveolar carbon dioxide ($PaCO_2$), (PaO_2), PEEP and FiO_2)], and treatments [ventilation, vasopressor, renal replacement therapy (RRT), and antibiotics].

Definition of PALBI

The following equation was used to calculate the PALBI score:[19,26] PALBI score = 2.02 x $\log_{10}$ bilirubin - 0.37 x ($\log_{10}$ bilirubin) - 0.04 x albumin - 3.48 x $\log_{10}$ platelets + 1.01 x ($\log_{10}$ platelets). PALBI score ≤ -2.53 was defined as grade I and > -2.53 as grade II.[27]

Outcome and follow-up

The endpoint of the present study was 30-day mortality after the ICU admission. Follow-up was initiated upon the ICU admission, and follow-up was terminated if the patient died within 30 days. The follow-up duration was 30 days.

Statistical analysis

Shapiro-Wilk test was conducted to assess the normality of the data. Normally distributed continuous data ($p > 0.05$) were presented as the mean ± standard deviation, and the comparison between death and alive groups using t-test. Continuous data with skewed distribution ($p \leq 0.05$) were described as median and quartile [M (Q1, Q3)] and the Wilcoxon rank-sum test was used to compare the two groups. Categorical data were described as numbers and percentages (n, %) and conducted using the chi-square test or Fisher's exact test (Supplementary Table 1).

To verify the robustness of results before and after the imputation of missing data, sensitivity analysis based on random forests was conducted (Supplementary Table 2). The missing-at-random (MAR) assumption was utilized to verify whether missing data were random (Supplementary Table 3). The results of MAR showed that all data had a minimum of $p < 0.05$; moreover, after the false discovery rate test, all p values were remained < 0.05, indicating that the missing data were missing at random. Covariates were screened using univariate Cox proportional hazards analysis. Univariate and multivariate Cox proportional hazards regression models were applied to examine the relationship between PALBI grade and the 30-day mortality with hazard ratios (HRs) and 95% confidence intervals (CIs). Model I was a crude model; model II was adjusted for age, sex, race, ICU type, atrial fibrillation, heart rate, SBP, DBP, respiratory rate, PEEP, GCS score, CCI, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor, and RRT. The associations were further assessed based on age, sex, severe liver disease, sepsis, pneumonia, and COPD. Kaplan-Meier curve was suggested for the survival probability of patients with ARDS with different PALBI grades. All statistical analyses were performed using *R* version 4.2.2 (Institute for Statistics and Mathematics, Vienna, Austria) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Bilateral $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of patients with ARDS

The screening process of patients with ARDS is depicted in Figure 1. Initially, 3,098 patients with ARDS with records of platelet counts, albumin, and bilirubin indicators were included. Among them, 250 patients were admitted to the ICU for < 24 h, and seven of them with missing survival information were excluded. A total of 2,841

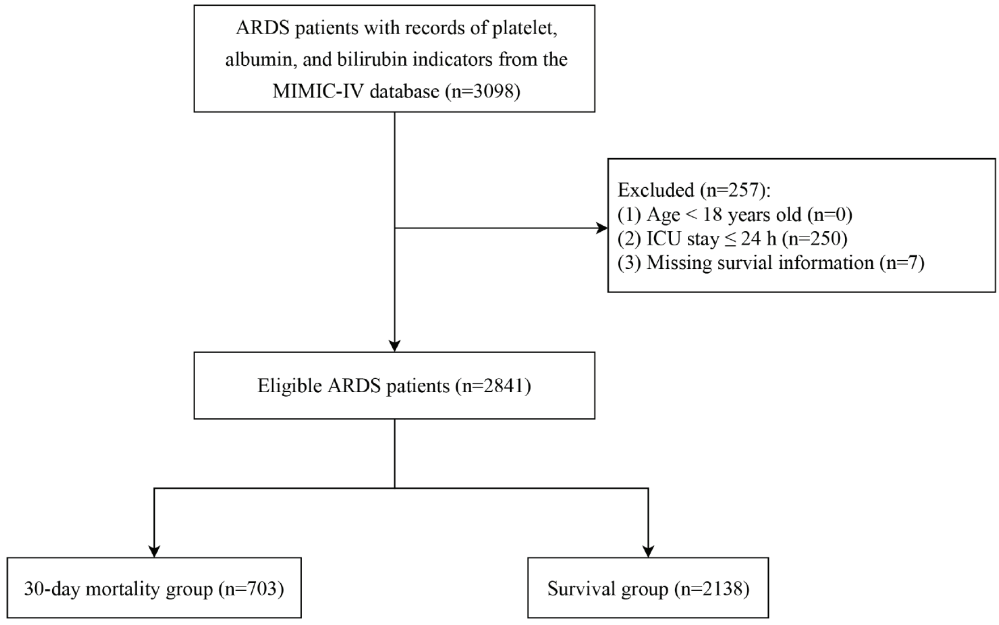

FIG. 1. Flowchart depicting subject screening.

ARDS, acute respiratory distress syndrome; MIMIC-IV, Medical Information Mart for Intensive Care; ICU, intensive care unit.

eligible patients with ARDS were finally included, with a mean age of 59.19 ± 16.01 years. Among them, 703 (24.74%) died within the median follow-up time of 30 (30, 30) days. Statistical differences in age, sex, race, ICU type, AKI stage, history of renal failure, history of atrial fibrillation, history of severe liver disease, history of metastatic cancer, heart rate, respiratory rate, SBP, DBP, PEEP, SOFA score, GCS score, CCI, albumin, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor, and RRT were observed between the 30-day mortality and survival groups. The proportion of PALBI grade II (> -2.53) in the 30-day mortality group was higher than that in the survival group (4.41% vs. 1.50%) (Table 1).

TABLE 1. ARDS Patients' Characteristics.

Variables	Total, (n =2841)	30-day mortality, (n = 703)	Survival group, (n = 2138)	Statistics	p
Age, year, mean ± SD	60 (49, 70)	65 (54, 76)	58 (48, 68)	Z=-9.31	<0.001
Gender, n (%)				χ^2=5,901	0.015
Female	1158 (40.76)	314 (44.67)	844 (39.48)		
Male	1683 (59.24)	389 (55.33)	1294 (60.52)		
Race type, n (%)				χ^2=38,876	
Other	740 (26.05)	180 (25.60)	560 (26.19)		
Unknown	455 (16.02)	164 (23.33)	291 (13.61)		
White	1646 (57.94)	359 (51.07)	1287 (60.20)		
ICU type, n (%)				χ^2=5,052	0.025
MICU/SICU	1840 (64.77)	480 (68.28)	1360 (63.61)		
Other	1001 (35.23)	223 (31.72)	778 (36.39)		
AKI stage, n (%)				χ^2=205,379	<0.001
0	484 (17.04)	55 (7.82)	429 (20.07)		
1	407 (14.33)	77 (10.95)	330 (15.43)		
2	1046 (36.82)	198 (28.17)	848 (39.66)		
3	904 (31.82)	373 (53.06)	531 (24.84)		

TABLE 1. Continued

Variables	Total, (n = 2841)	30-day mortality, (n= 703)	Survival group, (n= 2138)	Statistics	p
Renal failure, n (%)				χ^2=79,227	<0.001
No	1618 (56.95)	299 (42.53)	1319 (61.69)		
Yes	1223 (43.05)	404 (57.47)	819 (38.31)		
Atrial fibrillation, n (%)				χ^2=14,151	<0.001
No	2369 (83.39)	554 (78.81)	1815 (84.89)		
Yes	472 (16.61)	149 (21.19)	323 (15.11)		
Severe liver disease, n (%)				χ^2=8,035	0.005
No	2298 (80.89)	543 (77.24)	1755 (82.09)		
Yes	543 (19.11)	160 (22.76)	383 (17.91)		
Sepsis, n (%)				χ^2=0.186	0.667
No	1917 (67.48)	479 (68.14)	1438 (67.26)		
Yes	924 (32.52)	224 (31.86)	700 (32.74)		
Pneumonia, n (%)				χ^2=1,087	0.297
No	2036 (71.66)	493 (70.13)	1543 (72.17)		
Yes	805 (28.34)	210 (29.87)	595 (27.83)		
COPD, n (%)				χ^2=0.969	0.325
No	2228 (78.42)	542 (77.10)	1686 (78.86)		
Yes	613 (21.58)	161 (22.90)	452 (21.14)		
Metastatic cancer, n (%)				χ^2=47,458	<0.001
No	2670 (93.98)	623 (88.62)	2047 (95.74)		
Yes	171 (6.02)	80 (11.38)	91 (4.26)		
Vital signs					
Heart rate, BPM, mean ± SD	91 (78, 106)	94 (80, 109.5)	90 (77, 104)	Z=-3.98	<0.001
SBP, mmHg, mean ± SD	122 (106, 140)	120 (103, 138)	123 (107, 141)	Z=2.93	0.003
DBP, mmHg, mean ± SD	66 (56, 78)	65 (53, 77)	67 (57, 78)	Z=2.58	0.010
Respiratory rate, BPM, mean ± SD	18 (15, 22)	20 (16, 24)	18 (15, 22)	Z=-7.09	<0.001
Soring systems					
SOFA, M (Q_1, Q_3)	8 (5, 12)	11 (7, 15)	7 (5, 11)	Z=-14.7	<0.001
GCS, mean ± SD	15 (13, 15)	15 (10, 15)	15 (14, 15)	Z=3.5	<0.001
CCI, M (Q_1, Q_3)	2 (1, 4)	3 (1, 5)	2 (1, 4)	Z=-7.94	<0.001
Important laboratory parameters					
Bilirubin, µmol/l, M (Q_1, Q_3)	0.8 (0.4, 2.1)	0.8 (0.4, 2.8)	0.8 (0.5, 1.9)	Z=-1.73	0.0827
Albumin, g/l, mean ± SD	2.9 (2.5, 3.5)	2.9 (2.3, 3.4)	3 (2.5, 3.5)	Z=4.36	<0.001
Platelet, k/µl, M (Q_1, Q_3)	164 (107, 234)	164 (91.5, 243)	164 (110, 231)	Z=1.11	0.2657
WBC, k/µl, M (Q_1, Q_3)	11.2 (7.5, 15.9)	12.31 (8.05, 17.7)	10.9 (7.32, 15.3)	Z=-4.79	<0.001
Hemoglobin, g/dl, mean ± SD	10.6 (9, 12.3)	10.3 (8.65, 12.1)	10.65 (9.2, 12.4)	Z=3.36	<0.001
RDW, (%), mean ± SD	14.7 (13.6, 16.2)	15.2 (13.9, 16.8)	14.6 (13.5, 16)	Z=-6.71	<0.001
Hematocrit, (%), mean ± SD	31.9 (27.3, 37)	31.7 (26.4, 36.5)	32 (27.6, 37.2)	Z=1.62	0.105
BUN, mg/dl, M (Q_1, Q_3)	19 (13, 30)	24 (16, 38)	18 (12, 27)	Z=-11.2	<0.001
Glucose, mg/dl, M (Q_1, Q_3)	133 (107,174)	133 (106, 178)	133 (108, 172.75)	Z=0.063	0.9495
INR, ratio, mean ± SD	1.3 1.1,1.6)	1.4 (1.2, 1.8)	1.3 (1.1, 1.5)	Z=-7.39	<0.001

TABLE 1. Continued

Variables	Total, (n = 2841)	30-day mortality, (n = 703)	Survival group, (n = 2138)	Statistics	p
Microelement level					
Bicarbonate, mEq/l, mean ± SD	22 (18, 24)	20 (17, 23.5)	22 (19, 25)	Z=8.27	<0.001
Sodium, mEq/l, mean ± SD	139 (135, 141)	139 (135, 142)	138 (135, 141)	Z=-0.501	0.6162
Potassium, mEq/l, mean ± SD	4.1 (3.7, 4.6)	4.1 (3.7, 4.7)	4.1 (3.7, 4.6)	Z=-1.36	0.174
Chloride, mEq/l, mean ± SD	105 (101, 109)	105 (100, 109)	105 (102, 109)	Z=2.02	0.044
Blood gas analysis					
PH, mean ± SD	7.36 (7.29, 7.42)	7.34 (7.25, 7.42)	7.36 (7.3, 7.42)	Z=4.74	<0.001
SpO_2, (%), mean ± SD	99 (97, 100)	99 (95, 100)	100 (97, 100)	Z=5.48	<0.001
$PaCO_2$, (%), mean ± SD	39 (34, 45)	37 (32, 43)	40 (35, 45)	Z=6.09	<0.001
PaO_2, mmHg, M (Q_1, Q_3)	155 (100, 243)	135 (90, 219)	162.5 (104, 249)	Z=5.47	<0.001
FiO_2, (%), M (Q_1, Q_3)	50 (50, 100)	60 (50, 100)	50 (50, 100)	Z=-2.01	0.044
PEEP, mean ± SD	5 (5, 5)	5 (5, 5)	5 (5, 5)	Z=-4.48	<0.001
Ventilation, n (%)				χ^2=0.002	0.963
No	60 (2.11)	15 (2.13)	45 (2.10)		
Yes	2781 (97.89)	688 (97.87)	2093 (97.90)		
Vasopressor, n (%)				χ^2=149,931	<0.001
No	1131 (39.81)	142 (20.20)	989 (46.26)		
Yes	1710 (60.19)	561 (79.80)	1149 (53.74)		
RRT, n (%)				χ^2=35,711	<0.001
No	2447 (86.13)	558 (79.37)	1889 (88.35)		
Yes	394 (13.87)	145 (20.63)	249 (11.65)		
Antibiotics, n (%)				χ^2=2,480	0.115
No	377 (13.27)	81 (11.52)	296 (13.84)		
Yes	2464 (86.73)	622 (88.48)	1842 (86.16)		
PALBI grade, n (%)				χ^2=20,703	<0.001
≤ -2.53	2778 (97.78)	672 (95.59)	2106 (98.50)		
> -2.53	63 (2.22)	31 (4.41)	32 (1.50)		
Survival time, M (Q_1, Q_3)	30 (30.30)	5.16 (1.79, 12.17)	30 (30.30)	Z=50.94	<0.001
Severity of ARDS, n (%)				χ^2=38,281	<0.001
Mild	1877 (66.07)	405 (57.61)	1472 (68.85)		
Moderate	700 (24.64)	199 (28.31)	501 (23.43)		
Severe	264 (9.29)	99 (14.08)	165 (7.72)		
Ratio of p/f, mmHg, M (Q_1, Q_3)	265.00 (166.00, 393.33)	236.00 (142.00, 354.00)	281.00 (175.00, 404.00)	Z=-5,848	<0.001

T, t-test; Z, Wilcoxon-Mann-Whitney test; χ^2, chi-square test; SD, standard deviation; M, median; Q1, 1st Quartile; Q3, 3rd Quartile; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; BPM, beat per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale; CCI, Charlson Comorbidity Index; WBC, white blood cell count; RDW, red blood cell distribution width; BUN, blood urea nitrogen; PH, pondus hydrogenii; SpO_2, oxygen saturation; $PaCO_2$, pressure of alveolar carbon dioxide; PaO_2, pressure of alveolar oxygen; FiO_2, fraction of inspired oxygen; INR, international normalized ratio; RRT, renal replacement therapy; PALBI, platelet-albumin-bilirubin.

PALBI grade and mortality

Table 2 presents the association between PALBI grade and 30-day mortality in patients with ARDS. PALBI grade II (> -2.53) was significantly associated with higher odds of 30-day mortality in patients with ARDS (HR: 1.55, 95% CI: 1.05-2.29), after adjusting for age, sex, race, ICU type, atrial fibrillation, heart rate, SBP, DBP, respiratory rate, PEEP, GCS scores, CCI, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor, and RRT. The Kaplan-Meier curve exhibited the differences in the survival of patients with ARDS with various PALBI grades ($p < 0.0001$) (Figure 2). Moreover, regression results of other adjusted variates are shown in Supplementary Table 4.

PALBI grade and mortality in patients with ARDS based on different age, sex, and complications

Subgroup analysis based on age, sex, and complications was performed to examine whether the relationship between PALBI grade and 30-day mortality in patients with ARDS remains robust.

TABLE 2. Association of PALBI Grade with 30-day Mortality in Patients with ARDS.

	Model 1		Model 2	
PALBI grade	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
≤ -2.53	Ref		Ref	
> -2.53	2.43 (1.70-3.49)	<0.001	1.55 (1.05-2.29)	0.027

Model 1, crude model without adjustment; Model 2, adjustment for age, gender, race, ICU type, atrial fibrillation, heart rate, SBP, DBP, respiratory rate, PEEP, GCS score, CCI, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor, RRT; Ref, reference; HR, hazard ratio; CI, confidence interval; PALBI, platelet-albumin-bilirubin; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; PEEP, positive end-expiratory pressure; GCS, Glasgow Coma Scale; CCI, Charlson Comorbidity Index; WBC, white blood cell count; RDW, red blood cell distribution width; BUN, blood urea nitrogen; PH, pondus hydrogenii; SpO_2, oxygen saturation; $PaCO_2$, pressure of alveolar carbon dioxide; PaO_2, pressure of alveolar oxygen; FiO_2, fraction of inspired oxygen; INR, international normalized ratio; RRT, renal replacement therapy.

TABLE 3. Association of PALBI Grade with 30-day Mortality in ARDS Patients Stratified by Age, Gender, and Other Comorbidities.

Variables	PALBI grade	HR (95%CI)	p
Age ≥ 65 years	≤-2.53	Ref	
	>-2.53	2.30 (1.06-5.01)	0.036
Age < 65 years	≤-2.53	Ref	
	>-2.53	1.30 (0.81-2.10)	0.277
Gender (female)	≤-2.53	Ref	
	>-2.53	1.13 (0.57-2.24)	0.719
Gender (male)	≤-2.53	Ref	
	>-2.53	2.10 (1.29-3.44)	0.003
Severe liver disease (yes)	≤-2.53	Ref	
	>-2.53	1.07 (0.59-1.94)	0.831
Severe liver disease (no)	≤-2.53	Ref	
	>-2.53	1.87 (0.97-3.60)	0.062
Sepsis (yes)	≤-2.53	Ref	
	>-2.53	0.67 (0.24-1.88)	0.446
Sepsis (no)	≤-2.53	Ref	
	>-2.53	1.71 (1.11-2.64)	0.016
Pneumonia (yes)	≤-2.53	Ref	
	>-2.53	0.79 (0.33-1.86)	0.584
Pneumonia (no)	≤-2.53	Ref	
	>-2.53	1.86 (1.19-2.91)	0.007
COPD (yes)	≤-2.53	Ref	
	>-2.53	0.37 (0.08-1.69)	0.202
COPD (no)	≤-2.53	Ref	
	>-2.53	1.93 (1.28-2.91)	0.002

Ref, reference; HR, hazard ratio; CI, confidence interval; PALBI, platelet-albumin-bilirubin; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

TABLE 4. Sensitivity Analysis of PALBI Classification and Short-Term Mortality Risk in ARDS Patients.

	Model 1		Model 2	
Variates	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
PALBI grade				
≤ -2.53	Ref		Ref	
> -2.53	4.37 (2.40-7.93)	<0.001	1.93 (1.01-3.71)	0.048

HR: hazard ratio; CI: confidence interval; PALBI, platelet-albumin-bilirubin; Model 1, crude model; Model 2, adjusted age, gender, race, ICU type, atrial fibrillation, heart rate, SBP, DBP, respiratory rate, PEEP GCS, CCI, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor and RRT.

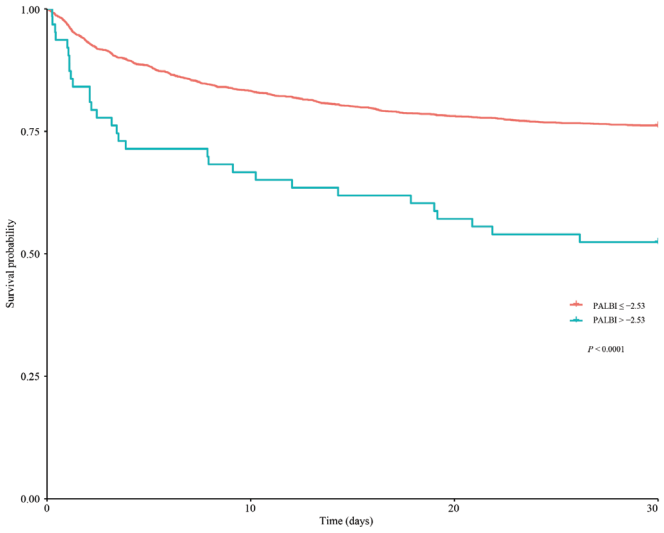

FIG. 2. Kaplan-Meier curve for data of patients with ARDS (with different PALBI grades).
ARDS, acute respiratory distress syndrome; PALBI, platelet-albumin-bilirubin.

After adjusting the age, sex, race, ICU type, atrial fibrillation, heart rate, SBP, DBP, respiratory rate, PEEP GCS, CCI, WBC, hemoglobin, RDW, BUN, bicarbonate, chloride, PH, SpO_2, $PaCO_2$, PaO_2, FiO_2, INR, vasopressor, and RRT, the results revealed that the elevated PALBI grade was related to higher odds of 30-day mortality in patients with ARDS aged ≥ 65 years (HR: 2.30, 95% CI: 1.06-5.01), males (HR: 2.10, 95% CI: 1.29-3.44), without sepsis (HR: 1.71, 95% CI: 1.11-2.64), without pneumonia (HR: 1.86, 95% CI: 1.19-2.91), and without COPD (HR: 1.93, 95% CI: 1.28-2.91). Detailed results are shown in Table 3.

Sensitivity analysis

Considering that patients with ARDS combined with severe liver disease may have a higher risk of mortality, 543 patients with severe liver disease were excluded from the study population. Then, sensitivity analysis was conducted to examine the relationship between PALBI grade and 30-day mortality in patients with ARDS. Results of the sensitivity analysis are shown in Table 4. After adjusting the confounding factors, patients with high PALBI grade had a high risk of 30-day mortality (HR: 1.93, 95% CI: 1.01-3.71), which was consistent with the main results of this study.

DISCUSSION

We found a significant association between high PALBI grade and poor short-term prognosis in patients with ARDS, especially among those aged ≥ 65 years, males, without sepsis, without pneumonia, and without COPD.

The PALBI grade is a comprehensive assessment index of liver function, calculated using total bilirubin levels, albumin levels, and platelet counts.[28] A study demonstrated that total bilirubin levels, albumin levels, and platelet counts were associated with poor outcomes in patients with ARDS.[12,15,16] Zheng et al.[16] reported that high bilirubin levels upon ICU admission were associated with the risk of death in patients with ARDS. Wang and Dai[12] indicated that lower platelet counts were related to high all-cause mortality in patients with ARDS. Hoeboer et al.[15] found that albumin levels < 20 g/l as well as a decline over a week were related to increased severity of ARDS. In addition, the PALBI grade has been used to assess liver function and prognosis in patients with HCC and cirrhosis.[26,29,30] Sonohara et al.[29] suggested that PALBI grade is an effective tool to assess perioperative risk in HCC keratectomy. Oikonomou et al.[30] found that the PALBI grade can predict the outcomes of patients with stable decompensated cirrhosis. Recently, a retrospective analysis reported that a high PALBI grade was related to poorer prognosis in patients with pancreatic head cancer.[21] However, to date, the association between PALBI grade and the prognosis of respiratory diseases remains unclear. We observed that high PALBI grade was associated with higher odds of 30-day mortality in patients with ARDS.

Furthermore, we examined the relationship between PALBI grade and 30-day mortality in the specific subpopulation. Our findings revealed that high PALBI grade was related to a higher risk of 30-day mortality in patients with ARDS who were males, without sepsis, without pneumonia, and without COPD. Conversely, the high PALBI grade was not associated with 30-day mortality in patients with ARDS with sepsis, pneumonia, and COPD. This might be due to changes in the levels of inflammatory or liver function markers with the progression of the disease. Previous studies suggest that the administration of endotoxin increased albumin synthesis and platelet counts in the early phase after a catabolic insult.[31,32] Early sepsis, pneumonia, and COPD may show higher PALBI grades, and early treatment may confer improved survival rates. In addition, the reduced sample size in the subgroups may potentially bias the results, and large-scale samples are required to further validate these findings.

The risk of short-term mortality in patients with ARDS may involve liver dysfunction, which is indicated by the PALBI grade. Previous studies also reported that patients with liver dysfunction are a high-risk group for ARDS, which involves multiple physiological processes such as the protein synthesis, respiratory host defense, and the interaction of systemic inflammatory response and metabolic processes.[9,33,34] Specifically, high bilirubin levels generate oxidative stress in the lung tissue and activate local inflammatory reactions, including cytokine release, and infiltration of alveolar macrophages and neutrophils, which have adverse effects on organs and cause serious irrecoverable injury in especial ARDS.[9,16,35] Animal experiments revealed that elevated bilirubin levels can directly cause injury to alveolar epithelial cells, generating cell cycle disruption and apoptosis.[36,37] Low platelet counts lead to aggregation of platelets, formation of platelet-leukocyte complexes, and release of molecules that enhance inflammation and cell adhesion, thereby negatively impacting the survival of patients with ARDS.[38-40]

Based on liver function, the PALBI grade is considered a comprehensive assessment indictor.[28] Our results show that high PALBI grade were related to higher odds of 30-day mortality in patients with ARDS. The PALBI grade is simple, objective, easy to obtain, and convenient to use, and hence, conducive to its application in clinical practice. Clinically, the PALBI grade may be used as a potential evaluation index for the bedside management of patients with ARDS. Physicians can better assess the risk of short-term mortality in patients with ARDS using the PALBI grade. This approach provides evidence for risk stratification management of patients with ARDS.

Several limitations of our study must be noted. First, due to the nature of a retrospective cohort study, some selection and reporting bias are inevitable. Second, this is a single-center study with limited representation, and the results in different ethnic populations must be further examined. Third, the MIMIC database does not have a comprehensive collection of drug information affecting the prognosis of patients with ARDS, which may affect the results. Fourth, the MIMIC database does not record the etiology of patients with ARDS; therefore, elucidating the association between the PALBI grade and short-term mortality in patients with ARDS with different etiologies requires further large-scale, well-designed prospective cohort studies.

In summary, we observed that high PALBI grade was associated with higher odds of 30-day mortality in patients with ARDS, which may help physicians to identify patients with ARDS at high risk of short-term mortality.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- D.Y.; Design- D.Y.; Supervision- D.Y.; Materials- D.Y., W.J., D.G.; Data Collection or Processing- D.Y., W.J., D.G.; Analysis or Interpretation- D.Y., W.J., D.G.; Writing- D.Y.; Critical Review- D.Y., W.J., D.G.

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