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Clinical paper

Monocyte programmed death-ligand 1 upregulation in early post-out-of-hospital cardiac arrest is associated with increased risk of acute respiratory distress syndrome

Le An [a,1], Rui Shao [a,1], Chenchen Hang [a], Xingsheng Wang [a], Luying Zhang [a], Hao Cui [a], Jingfei Yu [a], Zhenyu Shan [a], Ziren Tang [a,b,*]

[a] Department of Emergency Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China
[b] Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Beijing 100020, China

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ABSTRACT

Background: Out-of-hospital cardiac arrest (OHCA) is a major public health problem. Acute respiratory distress syndrome (ARDS) is a common condition in OHCA patients. We investigated the relationship between the expression of programmed death-1 (PD-1) related molecules and the development and prognosis of ARDS.
Methods: Between January 2021 and December 2023, post-resuscitated patients were screened for eligibility in the study. PD-1 related molecules expression was measured by flow cytometry at 48 h of admission in patients with OHCA. The prognostic variables were the development of ARDS during hospitalization and the 28-day patient mortality rate. We analyzed the relationship between the expression of PD-1-related molecules and the development of secondary ARDS in OHCA patients, and assessed the correlation of this expression with the prognosis of ARDS patients.
Results: In total, 107 consecutive OHCA patients were enrolled in this study. The median age of the enrolled patients was 60 years, with an age range of 53 to 67 years, and 71 % were male. Among the cardiac arrest patients, 44.8 % had a cardiac etiology, 30.8 % were witnessed, 17.8 % received bystander CPR, and 66.4 % had an initial rhythm of asystole. Our results showed that only monocyte ligand programmed death ligand-1 (PD-L1) expression was significantly elevated in the ARDS group of OHCA patients ($P < 0.001$). Among patients with ARDS, the expression of PD-L1 on monocytes in non-survivors was significantly higher than in survivors ($P < 0.05$). The Receiver operating characteristic curves analysis demonstrates that monocyte PD-L1 expression has predictive potential for the development and prognosis of ARDS. Multivariate logistic regression analysis showed that monocyte PD-L1 expression was an independent predictor of mortality in OHCA patients with ARDS.
Conclusions: This study indicates that patients with increased PD-L1 on monocytes after OHCA may be more likely to develop ARDS. The expression of PD-L1 on monocytes was an independent predictive factor for the incidence of ARDS and mortality rate in OHCA patients.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major global health concern, and remains one of the leading causes of mortality worldwide.[1] Despite advancements in cardiopulmonary resuscitation protocols, resuscitated patients often suffer from the post-cardiac arrest syndrome (PCAS), which is characterized by the systemic effects of ischemic reperfusion and persistent pathophysiological changes across multiple organs.[2,3] Acute Respiratory Distress Syndrome (ARDS) is a common and frequently fatal condition observed in Intensive Care Units.[4] Research suggests that more than half of OHCA patients may develop ARDS following resuscitation.[5,6] Although the precise pathophysiology of secondary ARDS in OHCA patients is not yet fully elucidated, immune cell regulation plays a pivotal role in its progression.[7,8].

The Programmed Death Ligand-1/Programmed Death-1 (PD-L1/PD-1) immune checkpoint pathway plays a pivotal role in regulating

* Corresponding author at: Department of Emergency Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China.
E-mail address: tangziren1970@163.com (Z. Tang).
[1] Le An and Rui Shao contributed equality to this work.

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immune function, serving to attenuate the immune response and influence the progression of diseases.[9,10] A significant increase in PD-L1 levels was observed in OHCA patients.[11] Patients with OHCA exhibited overexpression of PD-1 in the early period, leading to an imbalance in the Th1/Th2 ratio and increased levels of plasma IL-6 and IL-10.[12] Elevated levels of PD-L1 in the plasma were associated with the mortality in patients with ARDS.[13] A significant increase in PD-L1 expression in pulmonary endothelial cells and PD-1 expression on blood leukocytes not only induced significant indirect acute respiratory distress syndrome but also led to a significant mortality.[14] And gene deficiency of both PD-1 and PD-L1 improved pulmonary endothelial cells barrier function.[14] Elevated expression levels of PD-1/PD-L1 in OHCA patients may affect pulmonary endothelial cell barrier function, leading to a high incidence of ARDS post-resuscitation. However, few studies have explored whether the increased expression of PD-1/PD-L1 molecules in OHCA patients makes them more susceptible to developing ARDS.

Given the above considerations, the expression of PD-1 and PD-L1 in peripheral blood CD4 + T cells, CD8 + T cells, and monocytes (with only PD-L1 in monocytes being analyzed) during the early stages of OHCA was detected, and the relationship between the expression of these biomarkers and the development of ARDS as well as prognosis was analyzed.

Materials and methods

Study population

From January 2021 to December 2023, adult patients with OHCA admitted to the Emergency Intensive Care Unit (EICU) were screened for eligibility in the study. Only patients who survived for at least 48 h were included in the study to ensure sufficient time to develop ARDS. The criteria for ARDS were in accordance with the Berlin definition.[15] The following patients were excluded: those with a history of cancer, HIV infection, long-term glucocorticoid treatment, autoimmune disease, and those who developed ARDS within the first 48 h of admission. All patients received treatment in accordance with the international guidelines for cardiopulmonary resuscitation management. All patients received temperature control to maintain a target temperature of 33 °C for 24 h using surface cooling techniques. The study was approved by the Hospital Institutional Review Board and the Ethics Committee of Beijing Chaoyang Hospital (No. 2023-ke-780).

Data collection

Demographic and resuscitation data, and clinical and laboratory data were collected upon admission. Clinical data included age, gender, comorbidities, as well as the cause and characteristics of the cardiac arrest. Chest radiographs and computed tomography scans received during the treatment period were screened for pulmonary opacities which may represent ARDS. The diagnosis of ARDS was confirmed through blind assessments of chest radiographs and clinical data by two experienced critical care physicians. To ensure a robust process, an overlapping number of cases was reviewed by both reviewers. In cases of disagreement, a third expert physician reviewed the case, and consensus was reached through discussion. In addition, a control group of 24 age-matched healthy individuals without any history of disease was enrolled for comparison. To assess the severity of the cardiac event, the Sequential Organ Failure Assessment (SOFA) scores were calculated. The primary outcome of this study is the diagnosis of ARDS. And the secondary outcome is the assessment of the relationship between the expression of PD-L1 on monocytes and the mortality rate in OHCA patients who develop ARDS. Mortality is defined as death occurring within 28 days after hospital admission.

Flow cytometry

The ethylenediamine tetraacetic acid (EDTA) anticoagulant blood was collected from patients with OHCA within 48 h of admission and promptly transported to the research laboratory at a temperature of 4 °C. The flow cytometric analysis was performed by a researcher who was blinded to the corresponding clinical data. The analysis was carried out in accordance with the manufacturer's instructions, utilizing monoclonal antibodies and the relevant isotype controls. These included: 5 μl of BV421-labeled anti-PD1 (clone EH12.1), 20 μl of PE-labeled anti-PD-L1 (clone M1H1), 5 μl of APC-H7 labeled anti-CD3 (clone SK7), 5 μl of FITC-labeled anti-CD4 (clone OKT4), 20 μl of FITC-labeled anti-CD8 (clone RPA-T8), and 5 μl of APC-H7-labeled anti-CD14 (clone MφP9), all per 100 μl of whole blood. The samples were analyzed using a Gallios™ Flow Cytometer (Beckman Coulter, Brea, CA, USA) and the results were processed using Gallios Software Version 1.0 (Beckman Coulter). The results are presented as percentages and Mean Fluorescence Intensities (MFI).

Statistical analyses

The statistical analysis was conducted utilizing SPSS version 24.0 software (IBM, Chicago, IL, USA) and GraphPad Prism 6 (GraphPad, La Jolla, CA). For skewed-distributed data, the median and the 25th and 75th percentiles were used to express the variables. Multi-group comparisons were performed using the Kruskal–Wallis test, and between-group comparisons were performed using the Mann–Whitney *U* test. Qualitative parameters were evaluated using $\chi 2$ tests, and further analysis was performed using Continuity correction or Fisher's exact tests. The correlations were assessed using Spearman tests. Receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC) were analyzed. Multivariable logistic regression analyses were performed for each group to determine factors that could be considered independent predictors of clinical outcomes. All statistical tests were two-tailed, and P-value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

During the study period, a total of 139 OHCA patients were screened. After excluding patients with lung cancer (n = 6), autoimmune disease (n = 7), or those who received long-term glucocorticoid therapy (n = 3), as well as 11 patients who passed away within 48 h of admission and 5 patients who were lost to follow up. Eventually, 107 patients and 24 healthy volunteers were included in the study cohort. The majority of the initial rhythms recorded among OHCA patients were asystole. The median values of leukocytes, lymphocytes, and SOFA score were found to be significantly different in CA patients compared to healthy controls. Patients who developed ARDS had a longer hospital stay compared to those who did not (15 (13–16) days vs. 12 (11–15) days). The time from admission to the onset of ARDS was also calculated and found to be 9 (6–10) days. A summary of the baseline characteristics of the study cohort is presented in Table 1.

PD-1 and PD-L1 expression in patients with OHCA

The expression levels of PD-1 and PD-L1 on circulating CD4 + T cells, CD8 + T cells, and monocytes (PD-L1 only) were measured within 48 h after ROSC in patients. The percentages of monocytes expressing PD-L1 were significantly higher in OHCA patients compared to healthy controls (15.0 % (12.6 %-20.3 %) vs. 11.3 % (5.1 %-15.2 %), $P < 0.001$). Similar results were also observed when expressed as MFI (2.4 (2.1–2.6) vs. 1.8 (1.4–2.0), $P < 0.001$). The expression of PD-1 and PD-L1 on CD4 + T cells and CD8 + T cells was found to be not significantly different

Table 1
Baseline characteristics of the patients after out-of-hospital cardiac arrest.

Parameters	Control	Non-ARDS	ARDS	P value
n	24	42	65	–
Ages (years)	64 (53–69)	61 (49–66)	59 (53–68)	0.23
Male, n(%)	16 (66.7 %)	31 (73.8 %)	45 (69.2 %)	0.81
Comorbidities, n(%)				
Cardiovascular disease	–	19 (45.2 %)	25 (38.5 %)	0.49
Diabetes	–	9 (21.4 %)	12 (18.5 %)	0.71
Hypertension	–	15 (35.7 %)	26 (40.0 %)	0.66
Chronic respiratory disease	–	7 (16.7 %)	11 (16.9 %)	0.97
Cerebral infarction	–	5 (11.9 %)	9 (13.8 %)	0.77
Chronic kidney disease	–	8 (19.0 %)	7 (10.8 %)	0.23
Suspected Cardiac arrest etiology, n (%)				0.95
Cardiac	–	19 (45.2 %)	29 (44.6 %)	
Respiratory	–	12 (28.6 %)	16 (24.6 %)	
Other	–	6 (14.3 %)	11 (16.9 %)	
Unknown	–	5 (11.9 %)	9 (13.9 %)	
Witnessed cardiac arrest, n(%)	–	16 (38.1 %)	17 (26.2 %)	0.19
Bystander CPR, n(%)	–	6 (14.3 %)	13 (20.0 %)	0.45
Initial rhythm, n(%)	–			0.96
Asystole	–	28 (66.7 %)	43 (66.2 %)	
Pulseless electrical activity	–	14 (33.3 %)	22 (33.8 %)	
Leukocytes, $\times 10^9$/L	7.1 (5.6–7.9)	13.7 (11.1–16.4)	14.4 (8.9–16.6)	<0.001
Lymphocytes, $\times 10^9$/L	2.7 (2.4–3.1)	0.8 (0.5–1.2)	0.6 (0.4–0.8)	<0.001
PCT, g/mL	–	2.7 (0.6–7.4)	3.9 (1.8–8.3)	0.22
Monocytes PD-L1 expression (%)	11.3 (5.1–15.2)	13.3 (10.5–15.6)	16.5 (13.8–22.5)	<0.001
Monocytes PD-L1 expression (MFI)	1.8 (1.4–2.0)	2.2 (2.0–2.3)	2.5 (2.3–2.7)	<0.001
SOFA score	–	8 (7–10)	11 (8–14)	<0.001
Use of glucocorticoids, n(%)		14 (33.3 %)	32 (49.2 %)	0.11
Hospital length of stay (d)	–	12 (11–15)	15 (13–16)	0.001

Data are shown as median and interquartile range unless otherwise indicated. ARDS acute respiratory distress syndrome, CRP cardiopulmonary resuscitation, MFI mean of fluorescence intensities, PCT procalcitonin, PD-L1 programmed cell death receptor ligand-1, SOFA sequential organ failure assessment.

between patients with OHCA and healthy controls ($P > 0.05$). These results were shown in Table 1 and Supplementary materials (Table S1).

During hospitalization, 65 out of 107 patients developed ARDS according to the Berlin definition, whereas 42 patients did not develop ARDS. There were no significant differences between the groups in terms of age, gender, comorbidities, initial rhythm, leukocyte count, or PCT levels. The median values of witnessed CA, lymphocyte count, and SOFA score were significantly different in the ARDS group compared to the non-ARDS group (all $P < 0.05$). Additionally, the monocytes expressing PD-L1 were obviously different between the groups ($P < 0.001$, Fig. 1A and 1B). Similar results were also observed when expressed as the percentage of CD4 + PD-L1 expression and the MFI of CD8 + PD-L1 expression (all $P < 0.05$). The detailed results were presented in Table 1 and Supplementary materials (Table S1).

Patients with ARDS were further divided into survivors and non-survivors based on the 28-day mortality. There were 31 patients in the survivor group and 34 patients in the non-survivor group. The median SOFA scores were significantly different between non-survivors and survivors. Interestingly, among PD-1-related molecules, only the percentages of monocytes expressing PD-L1 were markedly elevated in non-survivors compared to survivors (20.0 % (15.7 %-31.8 %) vs. 14.5 % (12.6 %-16.6 %) $P = 0.001$, Fig. 1C). Similar results were observed when expressed as MFI (2.6 (2.4–3.2) vs. 2.4 (2.2–2.5), $P = 0.036$, Fig. 1C). The detailed data were shown in Table 2 and Supplementary materials (Table 2S).

Predictive potential of PD-L1 expression: ROC curve analysis

We established ROC curves and AUCs to evaluate the predictive qualities of PD-L1 expression. The ROC curve analysis showed that the AUC of the percentages of monocytes expressing PD-L1 for predicting ARDS in OHCA patients was 0.738. The AUC of the MFI of PD-L1 on monocytes was 0.758. These were slightly higher than the AUC of SOFA score (0.720). The detailed data were presented in Table 3 and Fig. 2A. The ROC curve analysis showed that the optimal threshold of the percentages of monocytes expressing PD-L1 for predicting ARDS was 14.7 % (sensitivity 67.7 %, specificity 71.4 %, positive predictive value (PPV) 78.6 %, negative predictive value (NPV) 58.8 %). The optimal threshold of the MFI of PD-L1 on monocytes was 2.34 (sensitivity 70.7 %, specificity 76.2 %, PPV 82.1 %, NPV 62.7 %).

Similarly, the AUC of the percentages of monocytes expressing PD-L1 and the MFI of PD-L1 on monocytes for predicting mortality was 0.762 and 0.736, which was slightly higher than that of SOFA score (0.711). The detailed data were showed in Table 3 and Fig. 2B. The best cutoff for predicting mortality in OHCA patients was 17.0 % for the percentages of monocytes expressing PD-L1 (sensitivity 70.6 %, specificity 77.4 %, PPV 77.4 %, NPV 70.6 %). And the optimal threshold of the MFI of PD-L1 on monocytes was 2.46 ng/ml (sensitivity 70.6 %, specificity 71.0 %, PPV 72.7 %, NPV 68.8 %).

PD-L1 expression as independent predictors of ARDS and mortality in OHCA patients

Univariate and multivariate logistic regression were used to identify the association of PD-L1 expression with ARDS and mortality in OHCA patients. After the univariate analysis, lymphocytes, witnessed CA, and SOFA scores were included in the multivariate logistic regression model. Binary logistic regression analysis revealed that the percentages of monocytes expressing PD-L1 were independent predictors of ARDS in OHCA patients (odds ratio (OR) = 1.131, 95 %CI: 1.002–1.276, $P = 0.046$), as did the MFI of PD-L1 on monocytes (OR = 4.821, 95 %CI: 1.081–21.506, $P = 0.039$).

Lymphocytes, witnessed CA, and SOFA scores were included in the multivariate logistic regression model to determine independent predictors of mortality in patients with ARDS. Multivariate logistic regression analysis revealed that the percentages of monocytes expressing PD-L1 was associated with the mortality (OR = 1.080, 95 % CI: 1.005–1.161, $P = 0.036$), as well as elevated the MFI of PD-L1 on monocytes (OR = 5.193, 95 %CI: 1.197–22.521, $P = 0.028$).

Discussion

This study demonstrates that in OHCA patients who developed ARDS during hospitalization, the expression of PD-L1 on monocytes was significantly increased in the early stages. The expression of PD-L1 on monocytes was an independent predictive factor for the incidence of ARDS and mortality rate in OHCA patients. However, the expression of PD-1 and PD-L1 on CD4 + T cells and CD8 + T cells did not exhibit significant clinical relevance.

PCAS is a complex set of pathophysiological changes that occur in patients after successful cardiopulmonary resuscitation, which can lead to multiple organ failure.[16] Effective management of PCAS is an essential aspect of most intensive care protocols to improve the prognosis of patients undergoing cardiac arrest.[2] PCAS is characterized by ischemia–reperfusion injury, which can lead to immune suppression and sustained inflammation.[17] Immune suppression increases the risk of

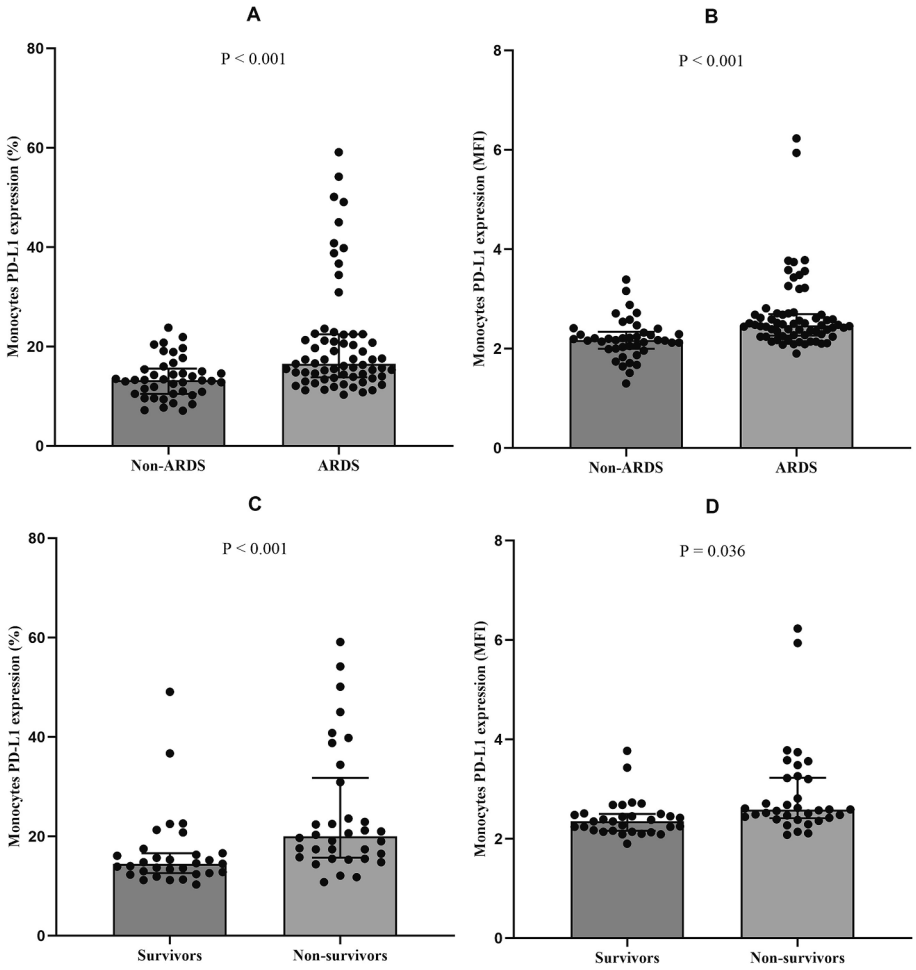

Fig. 1. PD-L1 expression in monocytes of out-of-hospital cardiac arrest patients. The median of the percentages of monocyte PD-L1 expression (A) or its MFI (B) was higher in the ARDS group than in the Non-ARDS group. Among patients with ARDS, the median of the percentages of monocyte PD-L1 expression (C) or its MFI (D) was increased in non-survivors than in survivors. The figure displays bar charts with error bars and scatter plots, where the error bars indicate the median with interquartile ranges.

infections and prolongs the recovery time from inflammatory responses.[18] ARDS, as a serious comorbidity of PCAS, shares similar pathophysiology with PCAS, further deteriorating the poor prognosis of patients after cardiopulmonary resuscitation.[19] Therefore, given the potential role of immunosuppression in patients with ARDS following OHCA, there is interest in identifying patients who may benefit from modulated immunotherapy.

In this study, we observed that monocyte PD-L1 expression was more susceptible to developing ARDS during hospitalization in patients after OHCA. Although Miho and colleagues demonstrated that the concentration of soluble PD-L1 (sPD-L1) was elevated in OHCA patients and correlated with the severity of PCAS, their study did not differentiate between patients with or without ARDS.[11] Our study showed that compared to healthy controls, OHCA patients had elevated monocyte PD-L1 expression, and ARDS patients had further elevation than non-ARDS patients after cardiopulmonary resuscitation. PD-L1 exhibits two distinct forms of expression, namely the membrane-bound form and the soluble form. Previous studies, such as those conducted by Miho and colleagues, have primarily focused on the measurement of sPD-L1 concentrations in plasma samples. In contrast, our study was designed to assess PD-L1 expression on the membrane-bound form in immune cells. The results of our investigation revealed a significant increase in PD-L1 expression on monocytes, while no clinical significance was observed with regards to PD-L1 expression on CD4 + T cells and CD8 + T cells. Through the more specific evaluation of PD-L1 expression on the membrane-bound form, our study provides a refined understanding of this immunomodulatory molecule in immune cells, which may serve as a valuable contribution to the advancement of basic research targeting PD-L1 expression.

Previous reports, conducted by Jing and colleagues, have demonstrated that low levels of PD-L1 indicated more severe disease and predicted a worse prognosis in patients with direct ARDS.[20] In contrast, Joanne and colleagues showed that PD-1/PD-L1 gene deficiency had a survival benefit in indirect ARDS.[14] These findings suggest that the immunosuppressive activity of PD-L1 may result in different or even opposing outcomes in different patient subgroups or diseases. Although Monaghan and colleagues proposed soluble PD-1 as a potential biomarker for extrapulmonary ARDS.[21] Our study did not find a significant difference in PD-1 expression on CD4 + T cells and CD8 + T cells. PD-1 is widely expressed on various immune cells including activated T cells, B cells, natural killer cells and so on.[22] Further research is needed to confirm whether PD-1 expression is elevated on other immune cells in patients with ARDS following OHCA.

Our study showed that PD-L1 expression on monocytes was significantly increased in non-survivors and it was independently associated with mortality in OHCA patients with ARDS. However, the immune status of patient needs to be evaluated based on multiple comprehensive indicators, and our study only provides part of the information. Immune suppression after cardiac arrest is indeed a complex issue, and current research is still actively exploring it. Some studies have suggested that

Table 2
Baseline characteristics of the patients with ARDS after out-of-hospital cardiac arrest.

Parameters	Survivors	Non-survivors	P value
n	31	34	–
Ages (years)	56 (53–67)	62 (54–68)	0.49
Male, n(%)	21 (67.7 %)	24 (70.6 %)	0.80
Comorbidities, n(%)			
Cardiovascular disease	10 (32.3 %)	15 (44.1 %)	0.33
Diabetes	4 (12.9 %)	8 (23.5 %)	0.44
Hypertension	14 (45.2 %)	12 (35.3 %)	0.42
Chronic respiratory disease	5 (16.1 %)	6 (17.6 %)	0.87
Cerebral infarction	3 (9.7 %)	6 (17.6 %)	0.57
Chronic kidney disease	3 (9.7 %)	4 (11.8 %)	0.90
Suspected Cardiac arrest etiology, n(%)			0.76
Cardiac	12 (38.7 %)	17 (50.0 %)	
Respiratory	9 (29.0 %)	7 (20.6 %)	
Other	6 (19.4 %)	5 (14.7 %)	
Unknown	4 (12.9 %)	5 (14.7 %)	
Witnessed cardiac arrest, n(%)	12 (48.4 %)	4 (41.2 %)	0.026
Bystander CPR, n(%)	8 (25.8 %)	5 (14.7 %)	0.42
Initial rhythm, n(%)			0.79
Asystole	20 (64.5 %)	23 (67.6 %)	
Pulseless electrical activity	11 (35.5 %)	11 (32.4 %)	
Leukocytes, $\times 10^9$/L	12.2 (8.2–17.1)	14.8 (9.2–14.8)	0.61
Lymphocytes, $\times 10^9$/L	0.7 (0.5–1.0)	0.5 (0.4–0.7)	0.030
PCT, g/mL	3.6 (2.6–5.6)	4.9 (1.5–9.5)	0.64
Monocytes PD-L1 expression (%)	14.5 (12.6–16.6)	20.0 (15.7–31.8)	<0.001
Monocytes PD-L1 expression (MFI)	2.4 (2.2–2.5)	2.6 (2.4–3.2)	0.001
SOFA score	9 (7–12)	12 (9–15)	0.003
Use of glucocorticoids, n(%)	13 (41.9 %)	19 (55.9 %)	0.39
Admission to ARDS (d)	9 (6–11)	7 (6–9)	0.15

Data are shown as median and interquartile range unless otherwise indicated. ARDS acute respiratory distress syndrome, CRP cardiopulmonary resuscitation, MFI mean of fluorescence intensities, PCT procalcitonin, PD-L1 programmed cell death receptor ligand-1, SOFA sequential organ failure assessment.

Table 3
Area under the curve of various parameters for predicting mortality in patients with ARDS after out-of-hospital cardiac arrest.

Variable	AUC	P value	95 % Confidence interval	
			Lower limit	Upper limit
the percentages of PD-L1 on monocytes	0.738	<0.001	0.641	0.834
MFI of PD-L1 on monocytes	0.758	<0.001	0.662	0.855
SOFA score	0.720		0.622	0.818
the percentages of PD-L1 on monocytes	0.762	<0.001	0.642	0.882
MFI of PD-L1 on monocytes	0.736	0.001	0.613	0.859
SOFA score	0.711	0.004	0.584	0.837

ARDS acute respiratory distress syndrome, AUC area under the curve, MFI mean of fluorescence intensities, PD-L1 programmed cell death receptor ligand-1, C1 the percentages of PD-L1 on monocytes in combination with the percentages of HLA-DR on monocytes, C2 MFI of PD-L1 on monocytes in combination with MFI of HLA-DR on monocytes.

immune suppression may be beneficial to some extent, such as reducing the excessive activation of inflammatory responses, but excessive immune suppression may also lead to an increase in complications such as infections.[23,24] Therefore, we cannot simply assume that immune suppression is completely beneficial or harmful, and it needs to be comprehensively evaluated based on the specific situation of the patient. Although we did not directly test all aspects of immune function in this study, the increased expression of monocyte PD-L1 is associated with the occurrence of ARDS and increased mortality, indicating that PD-L1 expression may be an indicator of abnormal immune regulation.

Limitations

The present study had several limitations. Firstly, our study reports a relatively high incidence of ARDS following out-of-hospital cardiac arrest (OHCA) at 61 %. The diagnosis of ARDS was based on the Berlin definition and confirmed by a blinded review of chest radiographs and clinical data by two critical care physicians. Our findings are in line with those of Elmer and colleagues, who reported a mean initial PaO_2:FIO_2 of 241, with values less than 300 in 65 % of patients in a mixed in-hospital and out-of-hospital cohort.[25] Secondly, our study demonstrated that monocyte PD-L1 expression was an independent predictive factor for the incidence of ARDS and mortality rates in OHCA patients. However, the magnitude of most associations in our study was relatively small. Future studies should focus on validating these findings in larger cohorts and exploring the combination of monocyte PD-L1 expression with other biomarkers or clinical parameters to enhance predictive power. Thirdly, in this study, we only conducted one flow cytometry examination on OHCA patients 48 h after admission. Further research on the dynamic changes of PD-L1 expression could provide more informative data. Finally, as an observational study, we included only patients surviving to 48 h for ARDS development. This may introduce bias as some who died within 48 h might have had high PD-L1 levels and developed ARDS if survived, potentially explaining the small effect size. Future research should use methods to account for competing risks and better assess the PD-L1 ARDS relationship considering death as a competing risk.

Conclusions

This study suggests that patients with increased PD-L1 expression on monocytes after OHCA are more likely to develop ARDS. The expression of PD-L1 on monocytes is an independent predictive factor for the incidence of ARDS and mortality rates in OHCA patients.

CRediT authorship contribution statement

Le An: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rui Shao:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chenchen Hang:** Writing – review & editing, Data curation, Conceptualization. **Xingsheng Wang:** Writing – review & editing, Data curation, Conceptualization. **Luying Zhang:** Writing – review & editing, Data curation, Conceptualization. **Hao Cui:** Writing – review & editing, Data curation, Conceptualization. **Jingfei Yu:** Writing – review & editing, Validation, Supervision, Resources. **Zhenyu Shan:** Writing – review & editing, Validation, Supervision, Resources. **Ziren Tang:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

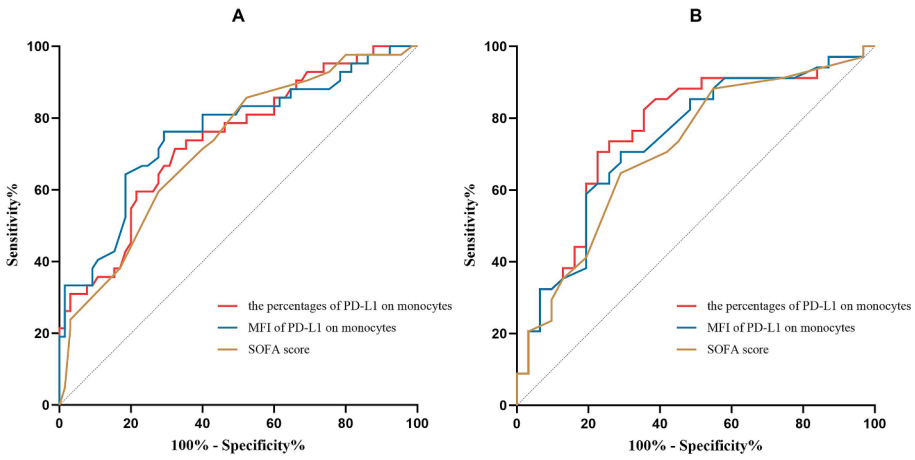

Fig. 2. Receive operating characteristic curve for predicting ARDS and mortality in patients with out-of-hospital cardiac arrest. Receive operating characteristic curve for predicting ARDS (A): the percentages of PD-L1 on monocytes (*Light Red*) 0.738, MFI of PD-L1 on monocytes (*blue-green*) 0.758, SOFA score (*Brown Yellow*) 0.720. Receive operating characteristic curve for predicting mortality among patients with ARDS (B): the percentages of PD-L1 on monocytes (*Light Red*) 0.762, MFI of PD-L1 on monocytes (*blue-green*) 0.736, SOFA score (*Brown Yellow*) 0.711. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100822.

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