Kynurenine pathway of tryptophan metabolism and hospital mortality in patients with acute respiratory distress syndrome: a prospective cohort study in metabolomics analysis

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Abstract

Background

Acute respiratory distress syndrome (ARDS) involves dysregulated immune-inflammatory responses following direct or indirect injury, characterized by severe hypoxemia respiratory failure and high mortality. At present, no conclusive diagnostic, predictive, or prognostic biomarkers have been developed for ARDS. Metabolites modulating inflammatory and immune responses may play a central role in the pathogenesis of ARDS. The aim of this study is to investigate the role of metabolic signatures in the clinical outcomes of patients with ARDS.

Methods

We conducted a prospective metabolomics study of 69 patients with ARDS. Metabolic profiling (on serum and urine) was performed and clinical variables were collected for analysis at day 1, day 3, and day 7 after ARDS onset. We also recruited 30 healthy control subjects (i.e., without significant comorbidities).

Results

Among the 69 ARDS patients, overall hospital mortality was 52.2%. Between day 1 and day 7 after ARDS onset, plasma kynurenine levels and the kynurenine/tryptophan ratio were significantly higher among nonsurvivors than among survivors (all $p < 0.05$). Urine metabolic profiling revealed a significantly higher prevalence of tryptophan degradation and higher concentrations of metabolites downstream of the kynurenine pathway among nonsurvivors than among survivors at the time of ARDS onset. Plasma kynurenine concentration was significantly correlated with organ failure. Cox regression models revealed that plasma kynurenine levels and the plasma kynurenine/tryptophan ratio at day 1 were independently associated with hospital mortality (adjusted HR = 1.017 [95% CI 1.003–1.032], $p = 0.017$ and adjusted HR = 1.761 [95% CI 1.204–2.576], $p = 0.004$, respectively). The 90-day hospital mortality of patients with high kynurenine levels (> 15.12 μM) at ARDS onset was significantly higher than that of patients with low kynurenine levels (≦ 15.12 μM) (66.7% vs. 25%, $p = 0.003$; log-rank test).

Conclusion

Activation of the kynurenine pathway was associated with mortality in patients with ARDS. Metabolic phenotypes and modulating metabolic perturbations of the kynurenine pathway could perhaps serve as prognostic markers or as a target for therapeutic interventions aimed at reducing morbidity and mortality in cases of ARDS.

Background

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome with alveolar injury secondary to clinical insults involving inflammatory cascades and immune responses. ARDS can lead to life-threatening refractory hypoxemia and/or multiple organ failure with mortality reaching 50% in severe cases [1, 2]. Currently, there are no reliable biomarkers by which to predict disease progression or guide the application of therapies for ARDS. Lung-protective mechanical ventilation remains the cornerstone of ARDS management [3].

Metabolomics refers to the high-throughput characterization of metabolites that play crucial roles in cellular physiology, inflammation, and the activation of immune cells by modulating the genome, epigenome, transcriptome, or proteome [4–6]. An association between metabolism and inflammatory or immune responses (i.e., metabolite-cytokine correlations) has also been observed in cases of the coronavirus disease 2019 (COVID-19) [7–9]. Metabolic derangement provides an objective means to identify biological endotypes in terms of molecular mechanisms and pathogenesis. Metabolomics can be used to assess the risk of developing ARDS, facilitate patient stratification, predict severity or progression, and predict responses to drugs or other

medical interventions (i.e., pharmacometabolomics). However, the results of recent metabolomic studies in ARDS have not been consistent [4, 10, 11]. It is believed that metabolomics could eventually be used as a therapeutic target by which to enhance the precision of strategies for the treatment of ARDS [4, 10–14].

Most of biogenic amines form through the decarboxylation of amino acids and could induce the production of reactive oxygen species (ROS), oxidative stress via the amine oxidase-mediated catabolic pathway, mitochondrial dysfunction and programmed cell death [15–17]. Kynurenine is a toxic metabolite of biogenic amines, which forms through the breakdown of tryptophan, an essential amino acid obtained entirely via dietary intake. The tryptophan-kynurenine pathway is involved in the regulation of inflammation, immunity, neuronal function, and intestinal homeostasis. This pathway tends to be accelerated in cases of infectious and inflammatory insults or immune response activation. It has also been implicated in a variety of diseases and pathological conditions, such as autoimmune disorders, cancer, and neurodegenerative diseases [15, 18–23]. Note that researchers have yet to elucidate the impact of the kynurenine pathway on the progression of ARDS, clinical outcomes, or mortality of ARDS patients.

Our objective in this prospective study was to use targeted metabolomics to examine the association between serial changes in metabolic profiles (amino acids and biogenic amines) and hospital mortality among patients with ARDS.

Methods

Study design and patients cohort

This prospective metabolomics study involving 69 ARDS patients was conducted from February 2017 to June 2018 in the medical ICUs at a tertiary care referral center: Chang Gung Memorial Hospital (CGMH) in Taiwan. ARDS was defined in accordance with the Berlin criteria [24]. The exclusion criteria included the following: age < 20 years, potentially confounding comorbidities, multiple organ failure refractory to therapy (i.e., a moribund condition), death within 3 days after ARDS onset, and failure to obtain informed consent. During the initial phase of ARDS, all of the patients were deeply sedated and paralyzed. Mechanical ventilator settings were collected during the use of a neuromuscular blockade. Healthy control subjects with no evidence of significant comorbidities were also recruited. The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201407524B0, 201801052A3, and 20181497B0).

Data collection

Demographic data, etiologies of ARDS, and major comorbidities were recorded. Arterial blood gas and mechanical ventilator settings were recorded at approximately 10 a.m. on day 1 after the onset of ARDS as well as on day 3 and day 7. Clinical and laboratory variables were recorded and Sequential Organ Failure Assessment (SOFA) scores were calculated at day 1, day 3, and day 7. We also collected the dates of hospital and ICU admission, mechanical ventilator initiation and liberation, date of ARDS diagnosis, ICU and hospital discharge, and time of death. Mechanical power was calculated using the following equation: mechanical power (Joules/minutes) (J/min) = 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure – 1/2 × driving pressure) [25, 26].

Sample collection and preparation

Plasma and urine samples were obtained from patients after fasting overnight (for at least 8 hours) at day 1, day 3, and day 7 after ARDS onset. Plasma and urine samples were also obtained from the healthy controls under the same dietary constraints.

Whole blood (10 ml) was collected under sterile conditions using an EDTA-coated tube, which was then centrifuged within 2 hours (3,000 *rpm*; 4°C; 10 min), whereupon the plasma was transferred into a 15 ml polypropylene tube. To separate cell debris, the plasma was centrifuged again at 3,000 *rpm* at 4°C for 10 min. After the second centrifugation, the plasma was aliquoted in an Eppendorf tube and stored at –80°C until assayed. Urine samples were centrifuged at 3,000 *rpm* at 4°C for 10 min with the supernatant collected in an Eppendorf tube and stored at –80°C until assayed (see Fig.S1, and sample collection and preparation in the Additional file 1).

Amino acids and biogenic amine analysis of plasma and urine samples

Amino acids and biogenic amines were respectively measured via ultra-high performance liquid chromatography and liquid chromatography-mass spectrometry. Urine samples were diluted with distilled water to a creatinine content of 100 μg/ml, as measured using an ultra-high performance liquid chromatography system. Pertinent details pertaining to the methods used in sample processing are provided in the Additional file 1.

Statistical analysis

Continuous variables are presented as mean and standard deviation for normally distributed variables or median and interquartile range for not normally distributed variables. A student *t*-test was used for the comparison of normally distributed data, and a Mann-Whitney *U* test was used for nonparametric data. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test for equal proportions or Fisher's exact test. The receiver operating characteristic (ROC) curve and Youden index were used to determine the cutoff to dichotomize continuous variables. Univariate analysis was used to identify risk factors associated with hospital mortality followed by the construction of Cox proportional hazard regression models with stepwise selection. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The probability of survival was analyzed using the Kaplan-Meier method and compared between groups using the log-rank test. Statistical analysis was performed using SPSS Statistics version 26.0, and statistical significance was considered by a two-sided *p* value of less than 0.05.

Results

Study patients

A total of 69 patients with ARDS and 30 healthy controls were enrolled in this prospective metabolomics cohort study. Overall hospital mortality among ARDS patients was 52.2%. Heat maps and volcano plot analysis revealed distinct quantitative differences between survivors and nonsurvivors in the metabolic phenotyping of amino acids and biogenic amines. Note that plasma kynurenine was the only metabolite with significantly higher values in nonsurvivors than in survivors (day 1 to day 7 after ARDS onset) (Fig. 1). The maximum Youden index value was used to categorize patients according to plasma kynurenine levels at day 1, using a cutoff of 15.12 μM: high plasma kynurenine group (45 patients; 65 %) and low plasma kynurenine group (24 patients; 35 %).

Comparisons of survivors and nonsurvivors

As shown in Table 1, there were no significant differences between survivors and nonsurvivors in terms of age, sex, or ARDS etiology. Body weight and body mass index were significantly higher among survivors than among nonsurvivors. A higher proportion of nonsurvivors were immunocompromised.

SOFA scores at day 1 were significantly higher among nonsurvivors than among survivors, and these values decreased between day 1 and day 7 among survivors but increased among nonsurvivors. At day 1, plasma kynurenine levels were significantly higher among patients than among healthy controls (25.1 ± 19.1 vs. 3.7 ± 0.6 μM, $p < 0.001$). Among nonsurvivors between day 1 and day 7, we observed a stepwise increase in the mean concentration of plasma kynurenine. Among survivors between day 1 and day 7, we observed a stepwise decrease in the mean kynurenine/tryptophan ratio. On all sampling days, plasma kynurenine levels and the plasma kynurenine/tryptophan ratio were both significantly higher among nonsurvivors than among survivors (all $p < 0.05$) (Table 1 and Fig. 1). Baseline (day 1) plasma kynurenine levels were significantly correlated with SOFA scores (Fig. 2).

There were no significant differences between the two groups in terms of ventilator settings at day 1 and day 7, with the exception of higher mechanical power and higher respiratory rates among nonsurvivors at day 7. Quantitative metabolic profiling of amino acids and biogenic amines between survivors and nonsurvivors (day 1 to day 7 after ARDS onset) is provided (see Table S1 and Table S2 in the Additional file 1).

Comparing patients with high and low plasma kynurenine levels

As shown in Table 2, no significant differences were observed between the high plasma kynurenine group and low plasma kynurenine group in terms of age, sex, body weight, or body mass index. Between day 1 and day 7, there was a stepwise decrease in SOFA scores in the low kynurenine group. SOFA scores were significantly lower in the low kynurenine group than in the high plasma kynurenine group (all $p < 0.05$). Between day 1 and day 7, plasma kynurenine/tryptophan ratios were significantly higher in the high plasma kynurenine group than in the low plasma kynurenine group. There were no significant differences between the two groups in terms of ventilator settings at day 1. The incidence of hospital mortality was significantly higher in the high plasma kynurenine group than in the low plasma kynurenine group (66.7% vs. 25%, $p = 0.003$).

Urine metabolite profiling: tryptophan degradation

The metabolic profiles of urine samples at day 1 revealed a significantly higher incidence of tryptophan degradation among nonsurvivors than among survivors (fold change 0.72; $p = 0.031$). All downstream kynurenine pathway metabolites were higher among nonsurvivors (day 1 and day 3) than among survivors (day 1 of ARDS onset), and many of the differences reached significance (Table 3). Fig. 3 presents a schematic illustration showing the kynurenine pathway of tryptophan catabolism with the altered metabolites highlighted.

Factors associated with hospital mortality

After adjusting for significant confounding variables, Cox proportional hazard regression models revealed a number of factors that were independently associated with an elevated risk of 90-day hospital mortality: immunocompromised status, SOFA score at day 1, plasma lactate level at day 1, plasma kynurenine level at day 1, and plasma kynurenine/tryptophan ratio at day 1. Hazard of death estimates obtained using plasma kynurenine/tryptophan ratio at day 1 were higher than estimates obtained using plasma kynurenine at day 1 (adjusted HR = 1.761 and 1.017, respectively; both $p < 0.05$). Plasma kynurenine levels of > 15.12 μM at day 1 were independently associated with higher 90-day hospital mortality (adjusted HR = 4.317 [95% CI 1.621–11.495]; $p = 0.003$) (Table 4). The overall 90-day survival rate was significantly higher among patients with lower plasma kynurenine values on day 1 (≦15.12 μM) than among those with higher plasma kynurenine values on day 1 (>15.12 μM) (75% vs. 33.3%; $p = 0.003$; log-rank test) (Fig. 4).

Discussion

Our main insight in this prospective targeted metabolomics study was that at the time of ARDS onset, plasma kynurenine levels and the plasma kynurenine/tryptophan ratio were both independently associated with the likelihood of hospital mortality. Our findings indicate that activation of the kynurenine pathway may play a role in pathogenesis and may therefore serve as a biomarker by which to predict clinical outcomes in cases of ARDS.

Kynurenine can exert immunosuppressive effects through the aryl hydrocarbon receptor, which suppresses the proliferation of effector T cells and natural killer cells and promote the activation of regulatory T cells. Increased kynurenines levels have been shown to alter cellular metabolism and cause cell death via the ROS pathway [15, 19–23, 27]. Under the effects of an inflammatory stimulus or immune system activation, proinflammatory cytokines and chemokines (particularly tumor necrosis factor-α and interferon-γ) can enhance the activity of indoleamine 2,3-dioxygenase (IDO), which is a negative regulator of inflammation and immunization. IDO, which is highly expressed in antigen-presenting cells (e.g., dendritic cells), catalyzes the first and main rate-limiting step in the kynurenine pathway. In this way, it contributes to the breakdown of tryptophan and the accumulation of kynurenine with corresponding effects on immunosuppression and immune tolerance [18–22, 27, 28]. In the current study, the mean concentration of plasma kynurenine was significantly higher among nonsurvivors than among survivors throughout the study period. In our Cox regression model, plasma kynurenine values at day 1 were independently associated with hospital mortality (HR = 1.017, $p = 0.017$). Urine metabolic profiling revealed higher tryptophan degradation and higher downstream kynurenine pathway metabolites among nonsurvivors at day 1, indicating activation of the kynurenine pathway.

The kynurenine-to-tryptophan ratio has been widely used to estimate the enzyme activity of IDO, where an elevated kynurenine/tryptophan ratio often indicates that the activation of IDO correlates with elevated neopterin levels (an indicator of cellular immune activation and oxidative stress) [8, 9, 18, 22, 29–31]. Kynurenine is a neurotoxic metabolite, and activation of the kynurenine pathway (assessed in terms of plasma kynurenine levels and the kynurenine/tryptophan ratio) was independently associated with acute brain dysfunction (delirium and coma) in mechanically ventilated patients [32]. Sepsis is the leading cause of ARDS, and one previous study reported that the kynurenine/tryptophan ratio was up to 9-fold and was significantly higher in patients with septic shock than in the two control groups (nonseptic, low blood pressure controls and normotensive healthy subjects). The kynurenine/tryptophan ratio was also strongly correlated with inotrope requirements [29]. The kynurenine pathway has also been implicated in tumor-associated immunosuppression, wherein IDO may promote the evasion of tumor cells from the immune system surveillance. The overexpression of IDO is associated with poor prognosis in a variety of cancers, and clinical trials on IDO inhibitors for cancer immunotherapy are currently underway [19, 21, 28, 33].

Researchers have not previously investigated the potential role of the kynurenine/tryptophan ratio or IDO activity in cases of ARDS. Our findings revealed that between day 1 and day 7, the mean kynurenine/tryptophan ratio (an index for IDO activity) was significantly lower among survivors than among nonsurvivors and that the ratio decreased over time. Cox regression models revealed that estimates of hazard of death obtained using the plasma kynurenine/tryptophan ratio at day 1 were higher than estimates obtained using plasma kynurenine at day 1, despite the fact that both factors were independently associated with 90-day hospital mortality (adjusted HR = 1.761 and 1.017, respectively; both $p < 0.05$). This is an indication that inflammatory signals during ARDS enhanced IDO activity, which subsequently activated the kynurenine pathway, thereby participating in pathogenesis and disease progression with a corresponding effect on clinical outcomes. It is possible that the kynurenine/tryptophan ratio or IDO activity could be used as a prognostic tool for patient stratification or for the development of drugs aimed at improving clinical outcomes of ARDS [28].

Recent studies described strong associations between metabolites including the kynurenine pathway of tryptophan metabolism and proinflammatory cytokines/chemokines (e.g., interleukin (IL)-1 and IL-6) in COVID-19 patients [7, 8, 34]. Targeting tryptophan metabolism was shown to modulate the release of proinflammatory cytokines by peripheral blood mononuclear cells isolated from rhesus macaques infected *ex vivo* with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]. These results indicate that by intervening in metabolic dysregulation, it may be possible to suppress the release of cytokines in COVID-19 patients. The kynurenine/tryptophan ratio was also significantly increased among patients infected with SARS-CoV-2 than among those without SARS-CoV-2 infection and healthy controls [8, 31]. Nonetheless, confirming the impact of the activation of the kynurenine pathway on the pathogenesis, disease progression, and clinical outcomes of COVID-19-related ARDS will require further study.

The most common cause of death among ARDS patients is multiple organ failure [1, 2]. In previous research, metabolites of the kynurenine pathway were dysregulated in animal models and clinical observational studies of acute kidney injury [35]. Elevated plasma kynurenine values and/or the kynurenine/tryptophan ratio are predictive of sepsis and multiple organ failure in patients suffering major trauma [36]. Kynurenine-3-monooxygenase is a key enzyme and drug target involved in the conversion of kynurenine into neuroactive metabolites of the immunoregulatory kynurenine pathway, including 3-hydroxykynurenine, which contribute to increased oxidative stress, cellular damage, and apoptosis through the production of ROS. Efforts to inhibit the release of kynurenine-3-monooxygenase have been shown to reduce 3-hydroxykynurenine levels to alleviate acute kidney injury, prevent multiple organ failure, and ameliorate histological changes in lung tissue consistent with ARDS [19, 21, 35, 37]. The IDO-kynurenine-aryl hydrocarbon receptor signaling pathway has also been shown to play an important role in inflammation and multiple organ injuries in cases of SARS-CoV-2 infection [7, 9].

Nonetheless, few reports have explored the links between the kynurenine pathway and multiple organ failure in ARDS. Our findings revealed that plasma kynurenine concentrations were significantly correlated with SOFA scores at the time of ARDS onset, and a Cox regression model revealed that kynurenine levels and SOFA score were both independently associated with hospital mortality. ARDS is characterized by substantial alveolar and systemic inflammation triggered by proinflammatory mediators and cytokines [1, 2]. Thus, it is reasonable to assume that in ARDS patients, proinflammatory cytokines during ARDS

promote IDO activity, thereby contributing to an imbalance between tryptophan and kynurenine leading to multiple organ failure and death.

This study was hindered by a number of limitations. First, all of the patients were from a single tertiary care referral center and therefore lacked external validation. This no doubt limits the generalizability and reliability of our findings. Furthermore, we selected unventilated healthy individuals (rather than ventilated ICU patients without ARDS) as our control group. This no doubt poses a potential confounder. Second, we did not examine the precise mechanism involved in activating the kynurenine pathway in the pathogenesis of ARDS. Third, our measurements of circulating cytokines (e.g., IL-6 or interferon-γ) were not integrated with metabolic profiling to identify the potential metabolite-cytokine relationships. Fourth, despite the fact that the kynurenine/tryptophan ratio tends to fluctuate under certain conditions, we used it as a surrogate for IDO activity (as in recent studies) and did not check the exact IDO values. Finally, ARDS is a heterogeneous syndrome with a complex pathogenesis, and the study groups were prone to diverse variations in comorbidities, nutritional status, as well as pharmaceutical and clinical interventions, all of which may have influenced the metabolic fingerprint (metabotypes) of individuals. We observed an association between the activation of the kynurenine pathway and hospital mortality in ARDS patients; however, the causal relationship has yet to be clearly determined.

Conclusion

In the current prospective study on patients with ARDS, plasma kynurenine levels and the plasma kynurenine/tryptophan ratio were both independently associated with hospital mortality. Future research should focus on the mechanism(s) underlying kynurenine pathway activation in the pathogenesis of ARDS. It will also be necessary to determine whether activation of the kynurenine pathway could be considered a biomarker by which to stratify subgroups and predict clinical outcomes. Researchers could also consider therapeutic interventions targeting metabolic dysregulation of the kynurenine pathway to alleviate disease progression and reduce mortality in cases of ARDS.

Abbreviations

ARDS
acute respiratory distress syndrome
CI
confidence interval
COVID-19
coronavirus disease 2019
HR
hazard ratio
ICU
intensive care unit
IDO
indoleamine 2,3-dioxygenase
IL
interleukin
ROS
reactive oxygen species
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
SOFA
Sequential Organ Failure Assessment

Declarations

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Authors' contributions

LCC, KCK, and MLC performed the conception and study design. LCC, HYT, CMF, HCH, and KCK performed the data acquisition. LCC, HYT, CMF, CJL and MLC were responsible for assembling samples and laboratory experiments. LCC, HYT, CMF, and MLC were responsible for statistical analysis and interpretation. LCC, KCK, and MLC assumed responsibility for drafting the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All datasets analyzed in this study are available from the corresponding author following a reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the principles stated in the Declaration of Helsinki. The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201407524B0, 201801052A3, and 21801497B0). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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Tables

Table 1
Background characteristics, clinical, and metabolic variables: healthy controls and ARDS patients

Characteristics	Healthy controls ($n = 30$)	ARDS			p
		All (n = 69)	Survivors (n = 33)	Nonsurvivors (n = 36)	
Age (years)	66.3 ± 8.9	65.2 ± 14.5	63.9 ± 12.4	66.2 ± 15.9	0.512
Male (gender)	24 (80%)	53 (75.7%)	24 (72.7%)	29 (78.4%)	0.582
Body weight (kg)	68.7 ± 10.1	60.4 ± 11.9	65.2 ± 10.6	56.2 ± 11.1	0.001
Body mass index (kg/m^2)		23.2 ± 4.4	24.8 ± 3.8	21.9 ± 4.4	0.006
Bacterial pneumonia		50 (72.5%)	22 (66.7%)	28 (77.8%)	0.302
Extrapulmonary sepsis		6 (8.7%)	3 (9.1%)	3 (8.3%)	1.0
Aspiration pneumonia		4 (5.8%)	1 (3%)	3 (8.3%)	0.616
Influenza pneumonia		7 (10.1%)	5 (15.1%)	2 (5.6%)	0.242
Pulmonary hemorrhage		2 (2.9%)	2 (6.1%)	0 (0%)	0.219
Hypertension		24 (34.8%)	8 (24.2%)	16 (44.4%)	0.095
Diabetes mellitus		22 (31.9%)	11 (33.3%)	11 (30.6%)	0.746
Chronic lung disease		14 (20.3%)	5 (15.2%)	9 (25%)	0.338
Chronic liver disease		8 (11.6%)	5 (15.2%)	3 (8.3%)	0.462
Chronic kidney disease		20 (29%)	6 (18.2%)	14 (38.9%)	0.069
Immunocompromised status		32 (46.4%)	10 (30.3%)	22 (61.1%)	0.015
SOFA score at day 1		9.5 ± 3.5	7.9 ± 2.8	10.9 ± 3.5	< 0.001
Lung injury score at day 1		2.91 ± 0.46	2.84 ± 0.46	2.98 ± 0.43	0.205
Kynurenine at day 1 (μM)	3.7 ± 0.6	25.1 ± 19.1	17.8 ± 10.4	31.7 ± 22.6	0.002
Kynurenine at day 3 (μM)		29.8 ± 25.2	19.4 ± 11.1	39.5 ± 30.6	0.001
Kynurenine at day 7 (μM)		29.3 ± 39.6	16.8 ± 11.0	42.2 ± 52.7	0.014
Kynurenine/tryptophan ratio at day 1		1.1 ± 0.8	0.8 ± 0.6	1.4 ± 0.9	0.002
Kynurenine/tryptophan ratio at day 3		1.2 ± 1.2	0.7 ± 0.5	1.6 ± 1.5	0.003
Kynurenine/tryptophan ratio at day 7		0.8 ± 1.0	0.5 ± 0.3	1.2 ± 1.3	0.013
WBC (10^3/μl)		12.3 ± 6.2	11 ± 5.1	13.4 ± 7	0.115

Values are expressed as count (percentage), mean ± standard deviation or median (25th–75th percentiles)

ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cells

[a] Mechanical power (J/min) was calculated as 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure – 1/2 × driving pressure). Peak inspiratory pressure was considered as a surrogate for plateau pressure if not specified

Characteristics	Healthy controls (n = 30)	ARDS			p
		All (n = 69)	Survivors (n = 33)	Nonsurvivors (n = 36)	
Segment (%)		82 ± 14	81 ± 14	83 ± 13	0.649
Band (%)		2 (0–5)	1 (0–4)	3 (1–5)	0.493
Lactate (mg/dl)		15.3 (10.2–20.9)	14 (9.7–17.7)	17.7 (11–22.1)	0.057
CRP (mg/l)		161 (109–263)	146 (101–248)	172 (115–261)	0.406
Procalcitonin (ng/ml)		6.3 (1.7–27)	5.4 (0.9–19.1)	6.9 (2.5–29.1)	0.272
PaO_2/FiO_2 (mm Hg) at day 1		164.5 ± 62.2	177.9 ± 64	152.5 ± 56.9	0.087
Mechanical power (J/min)[a]		19.7 ± 6.1	18.5 ± 4.8	20.8 ± 6.9	0.118
Tidal volume (ml/kg PBW)		8.5 ± 2.4	8.1 ± 1.8	8.8 ± 2.7	0.212
PEEP (cm H_2O)		11.0 ± 1.9	11.2 ± 2.1	10.9 ± 1.7	0.576
Peak inspiratory pressure (cm H_2O)		28.1 ± 5.4	27.3 ± 4.8	28.8 ± 5.6	0.253
Mean airway pressure (cm H_2O)		16.5 ± 3.0	16.4 ± 3.0	16.7 ± 2.9	0.662
Dynamic compliance (ml/cm H_2O)		30.0 ± 12.9	30.7 ± 12.1	29.4 ± 13.4	0.676
Total respiratory rate (breaths/min)		22.2 ± 4.2	21.8 ± 4.1	22.6 ± 4.3	0.445
SOFA score at day 7		8.8 ± 5.0	5.7 ± 3.2	11.9 ± 4.5	< 0.001
PaO_2/FiO_2 (mm Hg) at day 7		178.6 ± 89.5	213.2 ± 90.5	151.5 ± 75.8	0.004
Mechanical power (J/min)[a]		18.2 ± 8.8	14.1 ± 6.4	20.8 ± 9.2	0.005
Tidal volume (ml/kg PBW)		7.5 ± 2.8	6.9 ± 2.2	7.9 ± 3.1	0.246
PEEP (cm H_2O)		11.1 ± 2.8	10.9 ± 3.0	11.2 ± 2.5	0.674
Peak inspiratory pressure (cm H_2O)		28.4 ± 8.0	26.4 ± 7.1	29.7 ± 8.2	0.14
Mean airway pressure (cm H_2O)		17.7 ± 3.8	17.7 ± 3.2	17.7 ± 4.0	0.994
Dynamic compliance (ml/cm H_2O)		27.7 ± 14.8	29.4 ± 18.6	26.6 ± 11.2	0.51
Total respiratory rate (breaths/min)		22.4 ± 5.8	20.0 ± 5.5	23.9 ± 5.3	0.015

Values are expressed as count (percentage), mean ± standard deviation or median (25th–75th percentiles)

ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cells

[a] Mechanical power (J/min) was calculated as 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure – 1/2 × driving pressure). Peak inspiratory pressure was considered as a surrogate for plateau pressure if not specified

Characteristics	Healthy controls (n = 30)	ARDS			p
		All (n = 69)	Survivors (n = 33)	Nonsurvivors (n = 36)	
Duration of mechanical ventilator (days)		17 (7–30)	9 (7–21)	20 (11–34)	0.075
Length of ICU stay (days)		18 (9–37)	11 (9–31)	20 (11–38)	0.5
Length of hospital stay (days)		32 (19–56)	40 (21–60)	30 (13–47)	0.135
Values are expressed as count (percentage), mean ± standard deviation or median (25th–75th percentiles)					

ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, FiO_2 fraction of inspired oxygen, *ICU* intensive care unit, PaO_2 partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cells

[a] Mechanical power (J/min) was calculated as 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure – 1/2 × driving pressure). Peak inspiratory pressure was considered as a surrogate for plateau pressure if not specified

Table 2
Background characteristics, clinical variables, and outcomes as a function of plasma kynurenine at ARDS onset

Characteristics	Kynurenine at ARDS onset		*p*
	High (n = 45) (> 15.12 μM)	Low (n = 24) (≤ 15.12 μM)	
Age (years)	66.1 ± 15.2	62.4 ± 12.3	0.310
Male (gender)	37 (82.2%)	16 (66.7%)	0.145
Body weight (kg)	61.4 ± 10.9	59.7 ± 12.4	0.563
Body mass index (kg/m^2)	23.6 ± 4.1	22.9 ± 4.6	0.516
SOFA score at day 1	10.3 ± 3.3	7.8 ± 3.3	0.004
SOFA score at day 3	10.8 ± 3.9	7.0 ± 3.3	< 0.001
SOFA score at day 7	10.4 ± 5.0	5.8 ± 3.2	< 0.001
Lung injury score	2.9 ± 0.4	2.9 ± 0.5	0.717
Kynurenine at day 1 (μM)	32.9 ± 19.4	10.4 ± 3.1	< 0.001
Kynurenine at day 3 (μM)	38.2 ± 27.1	13.2 ± 6.4	< 0.001
Kynurenine at day 7 (μM)	38.5 ± 46.9	12.9 ± 7.4	0.002
Kynurenine/tryptophan ratio at day 1	1.4 ± 0.9	0.5 ± 0.2	< 0.001
Kynurenine/tryptophan ratio at day 3	1.5 ± 1.3	0.5 ± 0.3	< 0.001
Kynurenine/tryptophan ratio at day 7	1.1 ± 1.2	0.4 ± 0.2	0.001
WBC (×10^3/μl)	12.9 ± 6.6	11.3 ± 5.5	0.333
Segment (%)	82 ± 14	81 ± 13	0.678
Band (%)	3 (1–5)	1 (0–5)	0.636
Lactate (mg/dl)	15.1 (10.6–21.1)	15.6 (9.9–19.7)	0.698
CRP (mg/l)	158 (110–260)	171 (76–303)	0.850
Procalcitonin (ng/ml)	6.9 (2.4–27.7)	4.0 (0.4–18.3)	0.072
PaO_2/FiO_2 (mm Hg) at day 1	162.6 ± 61.3	172.4 ± 62.3	0.533
Mechanical power (J/min)[a]	19.9 ± 6.6	19.6 ± 5.1	0.825
Tidal volume (ml/kg PBW)	8.3 ± 2.7	8.6 ± 1.6	0.681
PEEP (cmH_2O)	11.2 ± 1.9	10.9 ± 2.0	0.574

Values are presented as count (percentage), mean ± standard deviation or median (25th–75th percentiles)

ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cells

[a] Mechanical power (J/min) was calculated as 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure – 1/2 × driving pressure). Peak inspiratory pressure was considered as a surrogate for plateau pressure if not specified

Characteristics	Kynurenine at ARDS onset		*p*
	High (n = 45) (> 15.12 μM)	Low (n = 24) (≤ 15.12 μM)	
Peak inspiratory pressure (cm H_2O)	28.6 ± 5.2	27.7 ± 5.4	0.497
Mean airway pressure (cm H_2O)	16.8 ± 2.8	16.2 ± 3.3	0.444
Dynamic compliance (ml/cm H_2O)	28.8 ± 12.6	31.3 ± 12.8	0.438
Total respiratory rate (breaths/min)	22.4 ± 4.3	21.9 ± 4.2	0.644
Duration of mechanical ventilator (days)	17.5 (8–34)	9 (7–20)	0.204
Length of ICU stay (days)	20 (9–38)	13.5 (8.3–33.8)	0.650
Length of hospital stay (days)	34 (20–59)	25 (16–53.3)	0.451
Hospital mortality, no. (%)	30 (66.7%)	6 (25%)	0.003
Values are presented as count (percentage), mean ± standard deviation or median (25th–75th percentiles)			
ARDS acute respiratory distress syndrome, *CRP* C-reactive protein, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cells			
[a] Mechanical power (J/min) was calculated as 0.098 × tidal volume × respiratory rate × (peak inspiratory pressure − 1/2 × driving pressure). Peak inspiratory pressure was considered as a surrogate for plateau pressure if not specified			

Table 3 Urine metabolites of tryptophan degradation at day 1, day 3, and day 7 after ARDS onset compared to survivors at day 1

Metabolites	Day 1		Day 3			Day 7		
	Nonsurvivors	*p*	Survivors	Nonsurvivors	*p*	Survivors	Nonsurvivors	*p*
	Fold change		Fold change	Fold change		Fold change	Fold change	
Picolinic acid	1.52	0.002	1.22	1.43	<0.001	1.45	1.79	0.139
Neopterin	1.87	0.003	1.09	1.67	0.044	1.06	2.85	0.003
Nicotinic acid or Quinolinic acid	1.47	<0.001	1.11	1.69	<0.001	1.21	2.00	0.017
3-Hydroxykynurenine	1.30	0.299	1.05	1.57	0.055	0.74	0.95	0.192
Kynurenine	1.19	0.392	1.33	1.86	0.062	1.44	1.20	0.478
3-Hydroxyanthranilic acid	1.20	0.383	1.15	1.39	0.215	2.30	2.31	0.982
Tryptophan	0.72	0.031	1.08	0.95	0.282	1.07	1.10	0.850
Xanthurenic acid	1.43	0.035	0.96	1.49	0.010	1.27	5.62	0.038
Kynurenic acid	1.97	<0.001	0.99	1.84	<0.001	1.21	2.81	0.003

Data were calculated by dividing the value of metabolites by the value of metabolites of survivors at day 1. *ARDS* acute respiratory distress syndrome

Table 4
Cox proportional hazard regression analysis of factors associated with 90-day hospital mortality

Variables	Univariate analysis		Multivariable analysis model 1		Multivariable analysis model 2		Multivariable analysis model 3	
	HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Age	1.010 (0.986–1.035)	0.414						
Body mass index	0.896 (0.827–0.971)	0.007						
Bacterial pneumonia	1.468 (0.670–3.213)	0.337						
Influenza pneumonia	0.463 (0.111–1.927)	0.290						
Hypertension	1.738 (0.906–3.335)	0.096						
Chronic kidney disease	1.880 (0.965–3.663)	0.064						
Immunocompromised status	2.073 (1.072–4.008)	0.030	3.284 (1.559–6.917)	0.002	2.730 (1.313–5.676)	0.007	2.963 (1.434–6.121)	0.003
SOFA score at day 1	1.218 (1.110–1.336)	< 0.001	1.136 (1.017–1.269)	0.024	1.173 (1.055–1.305)	0.003	1.130 (1.009–1.266)	0.034
Lung injury score at day 1	1.740 (0.865–3.501)	0.120						
WBC at day 1	1.000 (1.000–1.000)	0.201						
Lactate at day 1	1.024 (1.010–1.038)	0.001	1.033 (1.012–1.054)	0.002	1.018 (1.004–1.032)	0.014	1.032 (1.011–1.053)	0.003

CI confidence interval, *FiO_2* fraction of inspired oxygen, *HR* hazard ratio, *MP* mechanical power, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PIP* peak inspiratory pressure, *RR* respiratory rate, *SOFA* Sequential Organ Failure Assessment, *V_T* tidal volume, *WBC* white blood cells

The multivariable analysis models included continuous variables (age, body mass index, SOFA score, lung injury score, laboratory data and ventilatory parameters: MP, V_T/PBW, PIP, and total RR) and categorical variables (etiologies of ARDS and comorbidities). For the continuous variables, the hazard ratio means that the risk of hospital mortality increases or decreases per unit increase of these variables

Model 1: add kynurenine at day 1 as a continuous variable

Model 2: add kynurenine/tryptophan ratio at day 1 as a continuous variable

Model 3: add kynurenine at day 1 > 15.12 μM as a categorical variable

Variables	Univariate analysis		Multivariable analysis model 1		Multivariable analysis model 2		Multivariable analysis model 3	
	HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Procalcitonin at day 1	1.003 (0.997–1.008)	0.346						
PaO_2/FiO_2 at day 1	0.994 (0.988–0.999)	0.030						
MP at day 1	1.034 (0.985–1.086)	0.177						
V_T/PBW at day 1	1.097 (0.961–1.251)	0.170						
PIP at day 1	1.026 (0.969–1.086)	0.378						
Total RR at day 1	1.031 (0.956–1.112)	0.428						
Kynurenine at day 1	1.018 (1.006–1.032)	0.005	1.017 (1.003–1.032)	0.017				
Kynurenine/tryptophan ratio at day 1	1.785 (1.295–2.461)	< 0.001			1.761 (1.204–2.576)	0.004		
Kynurenine at day 1 > 15.12 μM	3.806 (1.579–9.179)	0.003					4.317 (1.621–11.495)	0.003

CI confidence interval, *FiO_2* fraction of inspired oxygen, *HR* hazard ratio, *MP* mechanical power, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PIP* peak inspiratory pressure, *RR* respiratory rate, *SOFA* Sequential Organ Failure Assessment, *V_T* tidal volume, *WBC* white blood cells

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Model 1: add kynurenine at day 1 as a continuous variable

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Figures

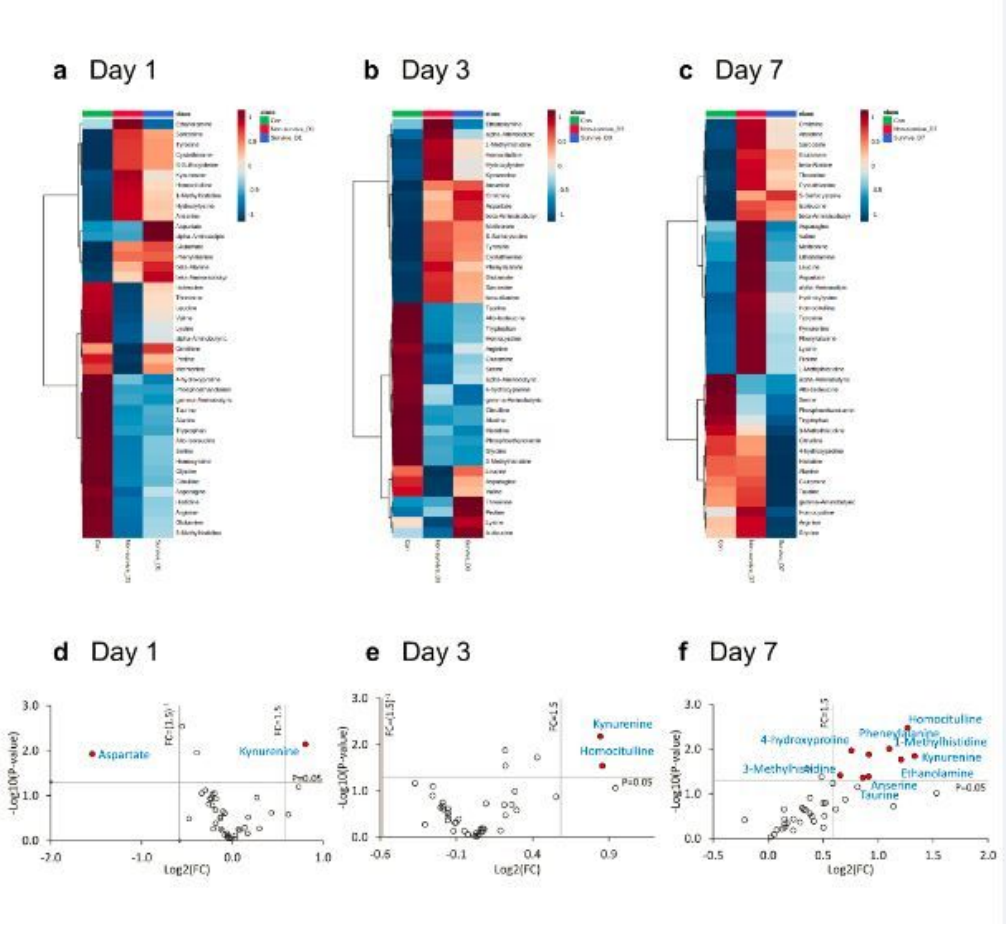

Figure 1

a, b, and c Heat maps of amino acids and biogenic amines among survivors and nonsurvivors of ARDS at day 1, day 3, and day 7 after ARDS onset, as well as healthy control subjects. **d, e, and f** Volcano plots of amino acids and biogenic amines comparing survivors and non-survivors of ARDS at day 1, day 3, and day 7 after ARDS onset. Data were selected at the cutoff point for *p* value < 0.05 and FC < 0.66 or > 1.5. ARDS, acute respiratory distress syndrome; FC, fold change

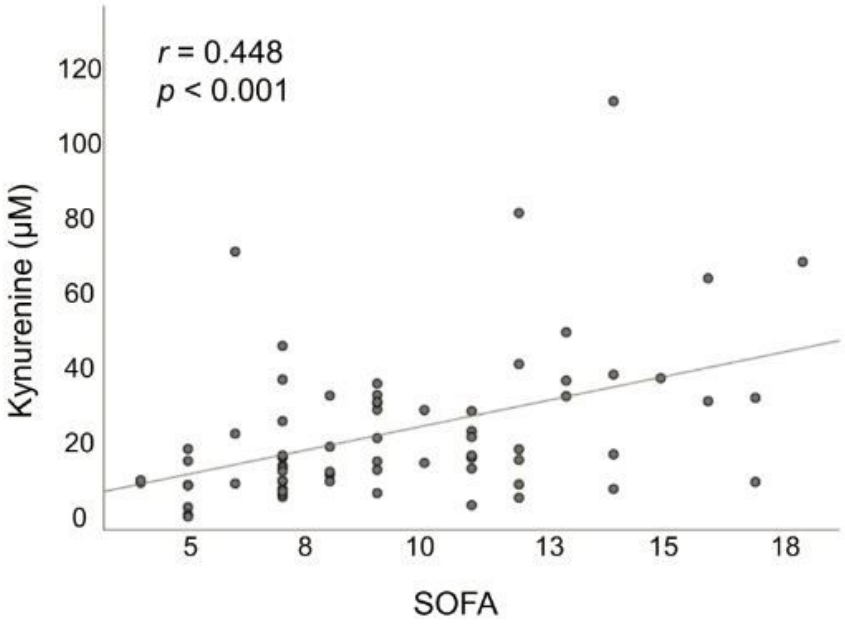

Figure 2

Association between plasma kynurenine levels and SOFA scores at day 1 after ARDS onset. ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment

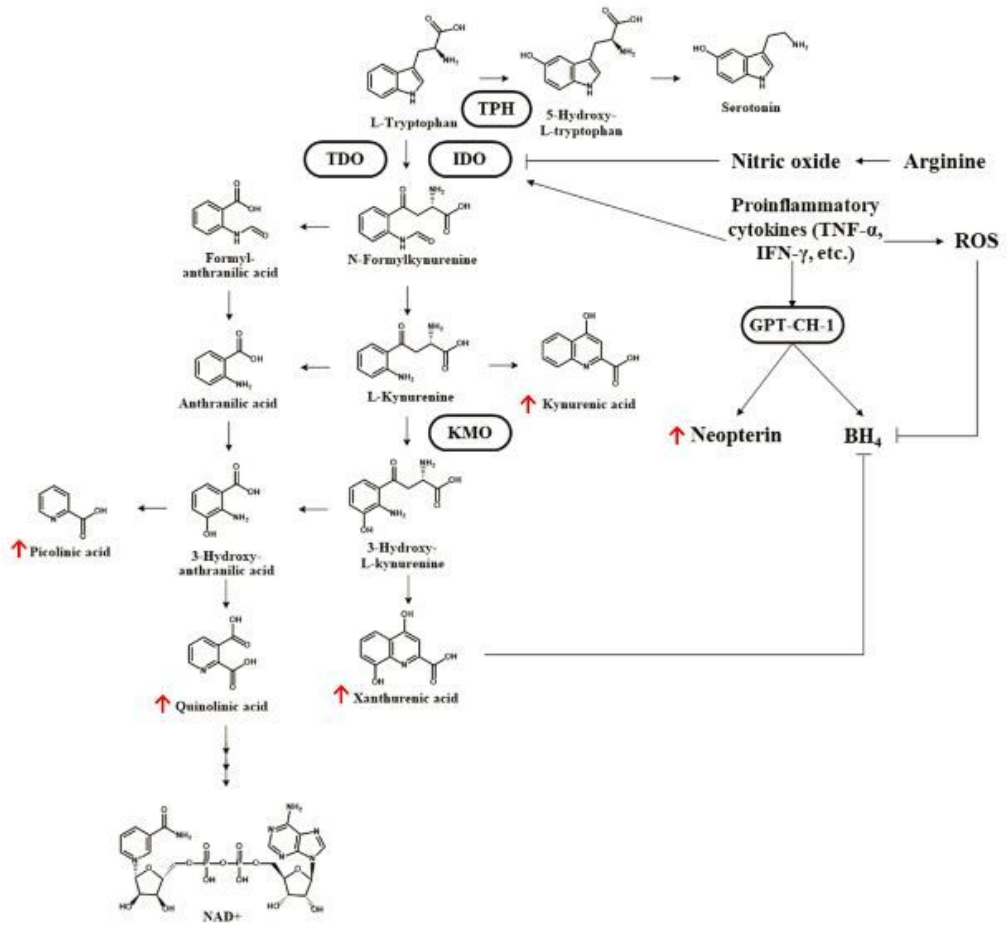

Figure 3

Kynurenine pathway of tryptophan catabolism. TPH, tryptophan 5-hydroxylase; TDO, tryptophan-2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; TNF-*α*, tumor necrosis factor-*α*; ROS, reactive oxygen species; GTP-CH1, guanosine triphosphate cyclohydrolase 1; KMO, kynurenine-3-monooxygenase; BH4, tetrahydrobiopterin; NAD, nicotinamide adenine dinucleotide

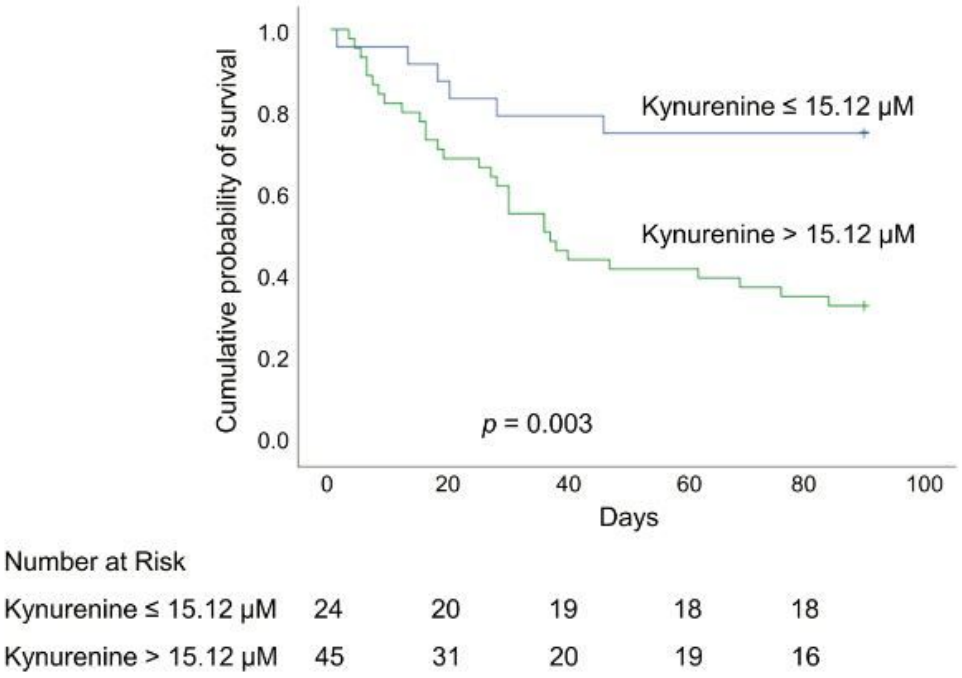

Figure 4

Kaplan-Meier 90-d survival curves of patients with ARDS, as stratified using an optimal cutoff value of plasma kynurenine (15.12 μM) at day 1. ARDS, acute respiratory distress syndrome

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalAbstract.jpg
- Supplementarymaterial.docx