Arterio-venous differences in glutamate concentration predict clinical outcomes in acute respiratory distress syndrome

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Research

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Abstract

Background

We aimed to explore whether the arterio-venous (A-V) differences in amino acids are useful for diagnosing and predicting acute respiratory distress syndrome (ARDS) outcomes, thereby guiding clinical therapy. The enrolled subjects included 36 adult patients with ARDS admitted in the intensive care unit (ICU) and 38 age- and sex-matched controls. Patients with ARDS were further divided into mild, moderate, and severe categories, and into survivor and non-survivor subgroups. Serum samples from the radial artery and jugular vein were collected on the first day following ICU admission, and the serum concentrations of 15 amino acids from the arterial and venous blood were measured by high performance liquid chromatography (HPLC) on the LC-10DVP system.

Results

We found that the arteriovenous (A-V) differences in glutamate (Glu) concentration in patients with ARDS were significantly greater than those in controls. Although no significant A-V differences were found in other amino acids between controls and patients with ARDS, surprisingly, survivors showed greater A-V differences in Glu concentration than non-survivors. Particularly, non-survivors who died within 2 weeks following ICU admission showed significantly less A-V differences in Glu concentration compared to those of survivors.

Conclusions

A-V differences in Glu concentration may be a biological marker for ARDS, with a significant association with mortality.

Introduction

Acute respiratory distress syndrome (ARDS), characterized by tachypnea, severe hypoxemia, and decreased respiratory compliance, is a common cause of respiratory failure [1]. Despite significant improvements in its clinical management and treatment, about 10% of all patients still require intensive care unit (ICU) admission worldwide, and the mortality rate remains high, at 30–40%, in most studies[1]. Currently, ARDS diagnosis is based on “the Berlin definition,” which includes clinical criteria. According to the oxygenation level (PaO_2/FiO_2), the degree of severity of patients with ARDS are diagnosed as mild (PaO_2/FiO_2: 200–300 mm Hg), moderate (PaO_2/FiO_2: 100–200 mm Hg), and severe ($PaO_2/FiO_2 \leq 100$ mm Hg) ARDS[2]. Even after the development and improvement of the Berlin diagnostic criteria, it is still a challenge to accurately diagnose ARDS or predict its prognosis. The best prediction method may be to combine clinical predictors with a variety of biomarkers[3]. Thus far, a large number of studies have found several biomarkers with the highest sensitivity and specificity useful in the diagnosis and

prognosis of ARDS[4]. However, no biomarker has yet been confirmed to diagnose or predict the outcome of ARDS, and none of those found has sufficient reliability for the clinical diagnosis of ARDS or the prediction of its prognosis. The lack of a specific biomarker for ARDS is undoubtedly one of the most important obstacles in the development of new treatment methods or strategies for ARDS. Consequently, researchers have called for the identification of specific markers that could lead to the early diagnosis of ARDS and accurately predict its outcome.

Blood is the main carrier of metabolites, including various nutrients (lipids and amino acids), hormones, and organic waste[5]. The circulatory system of the human body includes the arterial blood that delivers nutrition to the tissues and the venous blood that clears the byproducts of metabolism[5]. The blood circulation in the arteries and veins forms the basic part of the human anatomy, which plays an important role in maintaining the internal balance in all tissue stroma[5]. It is easier to obtain the venous blood, which can reflect the metabolism in specific organs[6]. However, the arterial blood, as a fluid, better reflects the average metabolic state of the body, before it is processed by any particular organ[7]. Moreover, the pulmonary blood flow (PBF) constitutes the entire output of the right ventricle and supplies the lung with mixed venous blood draining all the tissues of the body[8]. To some extent, the venous blood draining the whole body changes to arterial blood after gas and substance exchange in the alveoli in pulmonary capillaries. Therefore, comparing the differences between the venous blood flow into the lung and the arterial blood out of the lung will help to reveal how substances are released or consumed in the lung tissue. Generally, there is a difference in the metabolites in the arterial and venous blood[9–13]. However, the comprehensive biochemical characteristics of the difference between arterial and venous blood have not been reported. In critically ill patients like those with ARDS, either arterial or venous blood is usually available for sampling and measurement. Therefore, the question regarding the arterio-venous differences (A-V differences) in ARDS patients can be addressed.

Amino acids play an important role in the physiological and biochemical processes involved in the development of ARDS[14]. However, previous studies have not determined the exact relationship between amino acid levels and ARDS severity and outcomes. Hence, we performed global profiling of arterial and venous blood to assess the arterio-venous differences (A-V differences) in amino acids between control and ARDS patients. Therefore, we aimed to determine whether the arterio-venous differences in amino acids are useful predictors of ARDS diagnosis and outcome.

Patients And Methods

(1)Clinical data collection

This single-center retrospective study was conducted following the Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki.
The study was approved by the Institutional Ethical Review Board of the First Affiliated Hospital of University of South China, Hengyang, Hunan, China

Thirty-six patients with ARDS were enrolled during ICU admission and 38 control patients with other diseases, including chronic obstructive pulmonary disease (COPD), pulmonary infection, lung cancer, abdominal pain, chest and abdominal trauma hospitalized at the First Affiliated Hospital of University of South China between August 2018 and May 2019, and were matched based on age and gender. The inclusion criteria are as follows: (1) acute onset within 7 days; (2) bilateral pulmonary infiltrates consistent with pulmonary edema; (3) impaired oxygenation PaO2/FIO2 ratio < 300 mm Hg; (4) Impaired oxygenation not fully explained by cardiac failure; these ARDS patients were also stratified into mild (7 cases), moderate (8 cases), and severe (21 cases) groups according to the Berlin definition[2]. The exclusion criteria were as follows: (1) patients aged < 18 years; (2) pregnancy; (3) parenteral nutrition within 48 h after ICU admission; (4) history of diabetes or other metabolic-related diseases; (5) history of chronic liver disease; (6) human immunodeficiency virus (HIV) infection; and (7) refusal to take part in this study by the patients or their relatives. Demographic information; basic clinical laboratory testing such as hemoglobin (Hb) level; indexes of infection (white blood cell [WBC] count, C-reactive protein [CRP], and procalcitonin [PCT] levels); renal function (blood urea nitrogen [BUN] and serum creatinine levels); liver function (alanine transaminase [ALT], aspartate aminotransferase [AST], total bilirubin [TB], and direct bilirubin [DB] levels); medical comorbidities; and clinical outcomes were determined based on the patient's medical record. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Sequential Organ Failure Assessment (SOFA) scores were used to determine the initial severity of the illness during the first 24 h after admission. Patients were followed-up until discharge from ICU or based on a 28-day survival period.

(2)Amino acid determination

Blood samples for the determination of serum amino acids were collected from the radial artery and jugular vein of control and ARDS patients within 24 h after admission. The blood was centrifuged at 3,000 rpm for 15 min. The supernatants were stored at -80°C prior to analysis. The concentrations of 15 different kinds of amino acids (phenylalanine, alanine, methionine, glycine, glutamate, arginine, lysine, tyrosine, leucine, serine, threonine, aspartate, valine, isoleucine, and histidine) in serum were measured by high performance liquid chromatography (HPLC) on the LC-10DVP system (Shimadzu, Kyoto, Japan).

(3)Data collection and statistical analysis

All data were entered into the Microsoft Excel worksheet and statistical analyses were performed using SPSS version 23.0 software (IBM Corp., Armonk, N.Y., USA). The results for continuous variables with normal distributions were reported as the means ± standard deviations (SD). Qualitative variables were analyzed using the Chi-squared test, and quantitative variables were compared using the Student's t-test after being tested for normality with Levene's test. A two-sided p value < 0.05 was considered statistically significant.

Results

(1)General information

Between August 2018 and May 2019, a total of 36 patients with ARDS and 38 controls patients were selected following the relevant criteria. The ARDS group was further divided into mild (7 cases), moderate (8 cases), and severe ARDS (21 cases) subgroups, as well as into survivor (19 cases) and non-survivor (17 cases) subgroups. The non-survivor subgroup was again divided into ≤2 weeks (9 cases) and ≥2 weeks (8 cases) death subgroups (Fig. 1). As shown in Table 1, no significant differences were detected in age, sex, Hb level, and serum creatinine level between the controls and ARDS groups. WBC count, serum CRP, PCT, BUN, AST, ALT, TB, and DB levels were higher in the ARDS group than in the control group ($p < 0.05$). Additionally, in the ARDS group, the PaO2/FiO2, APACHE II, and SOFA scores were 123.5 ± 51.0; 18.6 ± 4.8; and 9.0 ± 2.5, respectively.

Table 1
Demographic and Clinical Characteristics of Patients

Amino acids (μg/ml)	Arterial			Venous		
	Control	ARDS	P value	Control	ARDS	P value
Phenylalanine (Phe)	1.56 ± 1.72	2.29 ± 1.48	0.0574	1.59 ± 1.81	2.40 ± 1.61	0.0495*
Alanine (Ala)	3.12 ± 4.05	3.16 ± 3.22	0.9635	3.46 ± 4.58	3.35 ± 2.98	0.9090
Methionine (Met)	0.18 ± 0.16	0.39 ± 0.70	0.0783	0.18 ± 0.17	0.44 ± 0.73	0.0396*
Glycine (Gly)	0.69 ± 0.54	0.61 ± 0.27	0.4515	0.70 ± 0.62	0.67 ± 0.41	0.8209
Glutamate (Glu)	2.70 ± 3.50	2.64 ± 1.8	0.9273	2.71 ± 3.92	2.25 ± 1.66	0.5199
Arginine (Arg)	1.56 ± 0.92	1.80 ± 1.33	0.3686	1.57 ± 0.93	1.97 ± 1.47	0.1614
Lysine (Lys)	1.55 ± 1.24	2.07 ± 1.61	0.1307	1. 62 ± 1.35	2.22 ± 1.61	0.0894
Tyrosine (Tyr)	1.06 ± 1.17	1.26 ± 1.10	0.4437	1.06 ± 1.11	1.28 ± 1.11	0.3860
Leucine (Leu)	1.36 ± 1.15	1.74 ± 1.17	0.1683	1.36 ± 1.24	1.82 ± 1.39	0.1485
Serine (Ser)	1.65 ± 2.01	1.37 ± 0.85	0.4503	1.60 ± 1.82	1.43 ± 0.91	0.633 1
Threonine (Thr)	4.06 ± 6.43	3.48 ± 3.63	0.6417	4.22 ± 6.73	3.56 ± 3.82	0.6126
Aspartate(Asp)	0.52 ± 0.39	0.67 ± 0.44	0.1331	0.52 ± 0.39	0.65 ± 0.42	0.1819
Valine (Val)	2.30 ± 1.82	2.908 ± 2.06	0.1884	2.25 ± 1.87	3.02 ± 2.45	0.1392
Isoleucine (Ile)	0.66 ± 0.47	0.91 ± 0.85	0.1275	0.67 ± 0.47	0.96 ± 1.06	0.1052
Histidine (His)	6.93 ± 3.90	6.78 ± 5.43	0.8973	7.24 ± 4.07	6.82 ± 5.00	0.6972

(2)The A-V differences in amino acid profiles between control and ARDS patients on ICU admission

We detected the levels of 15 different kinds of amino acids in the arterial and venous serum of control and ARDS patients. As shown in Table 2, there were no differences in the levels of all the 15 different kinds of amino acids detected in the arterial serum between control and ARDS patients. The level of

phenylalanine (p = 0.0495) and methionine (p = 0.0396) was increased in the venous serum of ARDS patients, while the levels of the remaining 13 amino acids in the venous serum showed no significant differences between control and ARDS patients. Since differences in amino acid levels between the venous and arterial blood could help to reveal how substances are released or consumed in the lung tissue, we further compared the A-V differences between control and ARDS patients. Table 3 shows that the A-V differences in Glu concentration in ARDS patients were significantly higher than those in controls (p = 0.002). We did not find any significant changes in the A-V differences of the remaining amino acid concentrations, comparing between control and ARDS patients. Since the venous blood draining the whole-body changes to the arterial blood after gas and substance exchange in the alveolar pulmonary capillaries, comparing the differences between venous and arterial blood could help to reveal how substances are released or consumed in the lung tissue. In ARDS patients, only the A-V differences in Glu concentration was greater when compared with controls.

Table 2
Amino acid profiles in arterial and venous blood of Patients

Amino acids	**Arterial- Venous(A-V)**		
(μg/ml)	**Control**	**ARDS**	**P value**
Phenylalanine (Phe)	-0.033 ± 0.355	-0.111 ± 0.560	0.4818
Alanine (Ala)	-0.332 ± 0.834	-0.188 ± 1.183	0.5492
Methionine (Met)	-0.003 ± 0.050	-0.047 ± 0.162	0.1159
Glycine (Gly)	-0.012 ± 0.163	-0.061 ± 0.315	0.4090
Glutamate (Glu)	-0.011 ± 0.581	0.391 ± 0.475	0.0020**
Arginine (Arg)	-0.009 ± 0.296	-0.175 ± 0.500	0.0890
Lysine (Lys)	-0.062 ± 0.389	-0.149 ± 0.519	0.4238
Tyrosine (Tyr)	0.002 ± 0.242	-0.020 ± 0.347	0.7550
Leucine (Leu)	-0.006 ± 0.298	-0.078 ± 0.383	0.3709
Serine (Ser)	0.053 ± 0.426	-0.063 ± 0.246	0.1659
Threonine (Thr)	-0.160 ± 0.646	-0.080 ± 0.626	0.5934
Aspartate(Asp)	-0.002 ± 0.186	0.018 ± 0.616	0.6092
Valine (Val)	0.048 ± 0.390	-0.109 ± 0.616	0.1989
Isoleucine (Ile)	0.0127 ± 0.149	-0.054 ± 0.309	0.2414
Histidine (His)	-0.309 ± 1.679	-0.034 ± 2.808	0.6485

Table 3 Amino acid Arterial-Venous differences (A-V) of Patients

Amino acids (μg/ml)	Arterial- Venous(A-V)		
	Control	ARDS	P value
Phenylalanine (Phe)	-0.033±0.355	-0.111±0.560	0.4818
Alanine (Ala)	-0.332 ±0.834	-0.188±1.183	0.5492
Methionine (Met)	-0.003±0.050	-0.047±0.162	0.1159
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Histidine (His)	-0.309±1.679	-0.034±2.808	0.6485

(3)Correlations between A-V differences in Glu concentration and the severity of clinical outcomes of ARDS patients

ARDS patients were divided into mild, moderate, and severe groups according to the Berlin definition. We found no significant changes in A-V differences in Glu concentration between mild, moderate, and severe patient groups (Fig. 2A). To explore the relationship between A-V differences in Glu concentration and outcome of patients, we compared the A-V differences in Glu concentration between survivors and non-survivors based on the 28-day survival period. A-V differences in Glu concentration in survivors (A-V = 0.615 ± 0.391, $p < 0.001$) and non-survivors (A-V = 0.3378 ± 0.306, $p = 0.026$) were both significantly higher than in control patients (A-V= -0.011 ± 0.581) (Fig. 2B). Surprisingly, we found that the A-V difference in Glu concentration in non-survivors was much lower than that in survivors ($p = 0.029$) (Fig. 2B). Further, to determine the relationship between Glu A-V differences and outcome of patients, we compared Glu A-V differences between survivors and non-survivors (patients who died within 2 weeks or after 2 weeks of ICU admission). Surprisingly, we found that patients who died within 2 weeks of ICU admission (A-V = 0.143 ± 0.259) had much lower Glu A-V differences than survivors (A-V = 0.615 ± 0.391, $p = 0.020$)

(Fig. 2C). However, there was no significant difference between survivors and non-survivors who died after 2 weeks of ICU admission. Our results showed that ARDS patients had a greater A-V difference in Glu concentration than controls, whereas in non-survivors, the difference was not as high as that in survivors. Thus, the A-V difference in Glu concentration showed a significant association with mortality in ARDS patients.

Discussion

Using HPLC, our study first showed the A-V differences in amino acid concentrations in controls and ARDS patients. In the 15 different amino acids that we detected in the arterial and venous blood, the A-V differences in only Glu concentration were significantly greater in ARDS patients than in controls. However, A-V differences in Glu concentration in ARDS patients showed no significant correlation with disease severity (grouped according to the ARDS Berlin definition). Furthermore, the result revealed that A-V differences in Glu concentration in ARDS survivors were considerably higher than in non-survivors, especially in non-survivors who died within 2 weeks of ICU admission. These results indicate that A-V differences in Glu concentration may be a biomarker for ARDS patients, especially to predict the outcome of ARDS.

Clinically, acute lung injury (ALI)/ARDS manifests as decreased lung compliance, severe hypoxemia, and bilateral pulmonary infiltrates, and is associated with a high mortality[1]. Diagnosis of ARDS are mainly based on clinical characterization. Numerous studies have focused on the identification of biomarkers, which can reflect pathophysiological mechanisms, to improve diagnosis, determining disease severity and prediction for outcome of ARDS. Researches already identified several biomarkers that are associated with the highest sensitivity and specificity for the diagnosis or outcome prediction of ARDS that have been investigated in blood, pulmonary edema fluid, and exhaled air[4]. In general, these are cell-specific for epithelial or endothelial injury or involved in the inflammatory or infectious response. But currently they are not reliable enough for clinical diagnosis of ARDS or prediction of its prognosis or have not yet been confirmed[4]. The lack of a specific biomarker to define, diagnose, monitor responsiveness to therapy or predict prognosis of ARDS has limited progress in developing novel treatments for ARDS. Thus, the discovery of a specific biological marker with early diagnostic significance is desirable.

Currently, it is an emerging area to identify metabolites including amino acid as clinically relevant biomarkers and potential therapeutic targets in several diseases, such as sepsis, diabetes, cancers and so on[14–18]. One study showed elevated levels of several metabolites, such as hippurate, L-phenylalanine, creatine, methionine, L-glutamate, and L-proline in bronchoalveolar lavage fluid (BALF) of patients with sepsis-induced ARDS compared to healthy controls[19]. Another study also showed that amino acid levels in the plasma differed in patients with acute exacerbation of COPD (AE-COPD), depending on the presence of bacterial infection. They claimed that specific amino acids (i.e., asparagine, citrulline, glutamine, histidine, serine, and threonine) have a potential utility as diagnostic markers to distinguish between bacterial and nonbacterial AE-COPD[20]. In another study, significant differences in the metabolomics and metabolic pathways between control and ARDS groups were observed. This study

suggests the potential utility of metabolomics to identify biomarkers that predict early ARDS onset, progression, severity, and prognosis[21] Another study focused on the plasma amino acid levels during the acute phase of endotoxin-induced lung injury in eight sheep, they found that norepinephrine, epinephrine, and alanine levels increased whereas that of isoleucine decreased. However, they did not determine the relationship between amino acid levels and ARDS severity and outcomes[14] Till now, the dynamics and clinically significant changes in amino acid levels in patients with ARDS are largely unknown.

To the best of our knowledge, to date, A-V differences in amino acid levels have not been extensively studied. In our study, we detected the A-V differences in amino acid levels between controls and ARDS patients. We found that A-V differences in Glu concentration in ARDS patients were significantly greater than in controls; however, the differences were not significant for other amino acids we study. Importantly, survivors showed greater A-V differences in Glu concentration than non-survivors, while non-survivors that died within 2 weeks following ICU admission showed significantly smaller A-V differences in Glu concentration than survivors. These results indicate that the A-V differences in Glu concentration can be a biological marker for ARDS and for outcome prediction. We tried to understand the higher A-V differences in Glu concentration in ARDS patients than in non-survivors. A-V difference in Glu concentration represents the arteriovenous difference in the levels of Glu (arterial level of Glu-venous level of Glu). Generally, venous blood becomes arterial blood in the lungs. Thus, to some extent, the A-V differences in substances can reveal how substances are released or consumed in the lung tissue. Our previous research detected 17 kinds of amino acids (phenylalanine, alanine, methionine, glycine, glutamate, arginine, lysine, tyrosine, leucine, serine, threonine, aspartate, valine, isoleucine, and histidine) in BALF of mice. The results showed that only Glu and glycine were increased in BALF of BLM-induced lung injury mice compared to the saline control group[22]. This research indicated that endogenous Glu and glycine may be selectively released from the lungs at the beginning of BLM-induced acute lung injury. If Glu is released from the injured lungs, it will also increase the Glu level in the arteries. Thus, we hypothesized that when the lung gets injured, cells selectively release Glu from the lungs to the blood or alveolar, which is consistent with the increased level of Glu in BALF of injured lungs as well as in arteries. System x(c)- is a cysteine/Glu transporter, with two subunits-4F2hc and the function unit of x (c)- system (xCT). At physiological conditions, system x(c)- mediates the release of Glu while it uptakes cysteine, which is essential for maintaining intracellular glutathione levels and cellular defenses against oxidative stress[23]. Previous researches suggested that xCT is upregulated in injured lung tissues induced by paraquat and plays a protective role against oxidative stress and lung injury[24]. As we detected in this study, ARDS patients had higher A-V differences in Glu concentration while that in non-survivors was much lower than for the survivors. We hypothesized that System x(c)- is upregulated in injured lung tissue to promote the uptake of cysteine and the release of Glu. This is important for the synthesis of glutathione, protecting the patients from oxidative stress-induced injury. System x(c)- function in non-survivors may be damaged, resulting in decreased release of Glu from the lung tissue, leading to the lower level of Glu in the arterial blood; which is consistent with the lower A-V differences in Glu concentration in non-survivors. A-V differences in Glu concentration in non-survivors were much lower

than those of survivors. This may indicate a reduction in the uptake of cysteine and glutathione synthesis, causing insufficient capacity of antioxidants in the lung cells of non-survivors.

Our study has several limitations that should be addressed. First, the results were obtained from a study population with a relatively small sample size; hence, the results will need to be confirmed using a larger sample size. Second, due to the limitation of clinical sampling, it was really difficult to obtain pulmonary arterial and venous blood. The blood from the radial artery and jugular vein that we collected could not fully represent the blood flowing in and out of the lung completely; thus, our results may not have fully determined the relationship between lung injury and A-V differences in Glu concentration. Third, we hypothesized that System x(c)- plays an essential role in the A-V differences in Glu concentration between controls and ARDS patients. However, we did not detect the level of xCT and glutathione in the patients. Further research is needed to clarify the mechanism and significance of releasing Glu from the lung. Furthermore, we did not show the relationship between long-term consequences in ARDS survivors and A-V differences in amino acid levels.

Conclusion

This is the first study to demonstrate that the A-V differences in Glu concentration in ARDS patients are significantly greater than those in controls. These differences can be used as a biological marker to predict the ARDS outcome. This can facilitate improved ARDS management and outcome prediction. Moreover, we hypothesized that greater A-V differences in Glu concentration in patients is an important biomarker which can indicate an endogenous protective factor preventing mortality or prolonging survival. The decreased A-V differences in Glu concentration in patients with poor prognosis may result from damaged System x(c)- or decreased xCT level in the lung, which needs further investigation.

Abbreviations

AECOPD, acute exacerbation of COPD, ALI, acute lung injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARDS, acute respiratory distress syndrome; A-V, arterio-venous; BALF, bronchoalveolar lavage fluid; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DB, direct bilirubin; G, glutamate; Hb, hemoglobin; HPLC, high performance liquid chromatography; ICU, intensive care unit; PBF, pulmonary blood flow; PCT, procalcitonin; TB, total bilirubin; WBC, white blood cell; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment

Declarations

Ethical Approval and Consent to participate

The study was approved by the Institutional Ethical Review Board of the First Affiliated Hospital of University of South China, Hengyang, Hunan, China and informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

Conceptualization, Ziqiang Luo; Data curation, Min Shao and Yan Zhou; Formal analysis, Fan Zhan and Baoxing Wen; Funding acquisition, Ziqiang Luo; Investigation, Fan Zhan and Yan Zhou; Methodology, Min Shao and Yan Zhou; Project administration, Ziqiang Luo; Resources, Fan Zhan, Haipeng Chen and Yujia Qiu; Software, Haipeng Chen and Yan Zhou; Supervision, Ziqiang Luo and Yanhong Huang; Validation, Yan Zhou; Visualization, Ziqiang Luo and Yanhong Huang; Writing – original draft, Fan Zhan and Yan Zhou; Writing – review & editing, Ziqiang Luo and Yan Zhou. All authors have read and agreed

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Figures

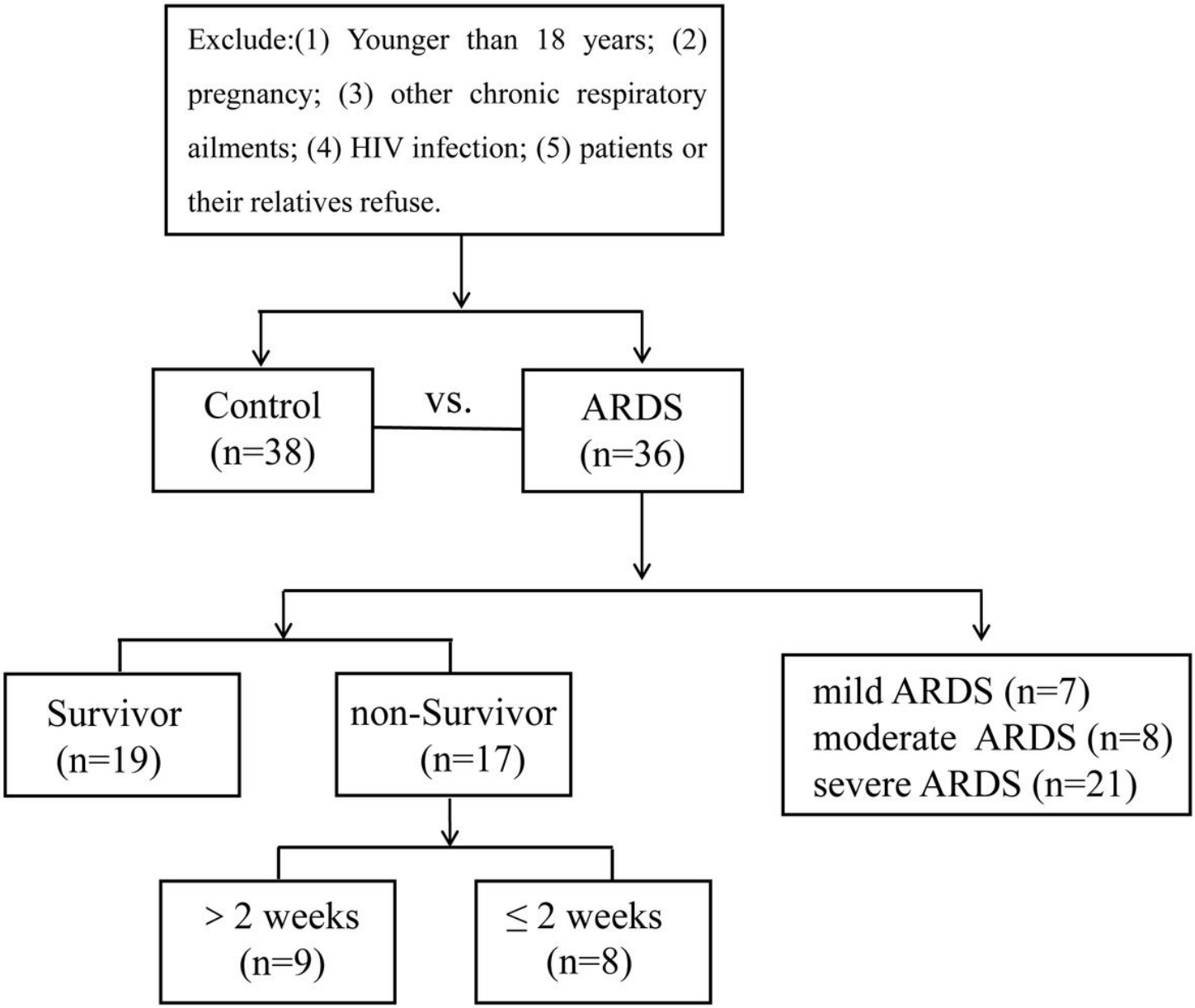

Figure 1

Flowchart of patient selection process for study

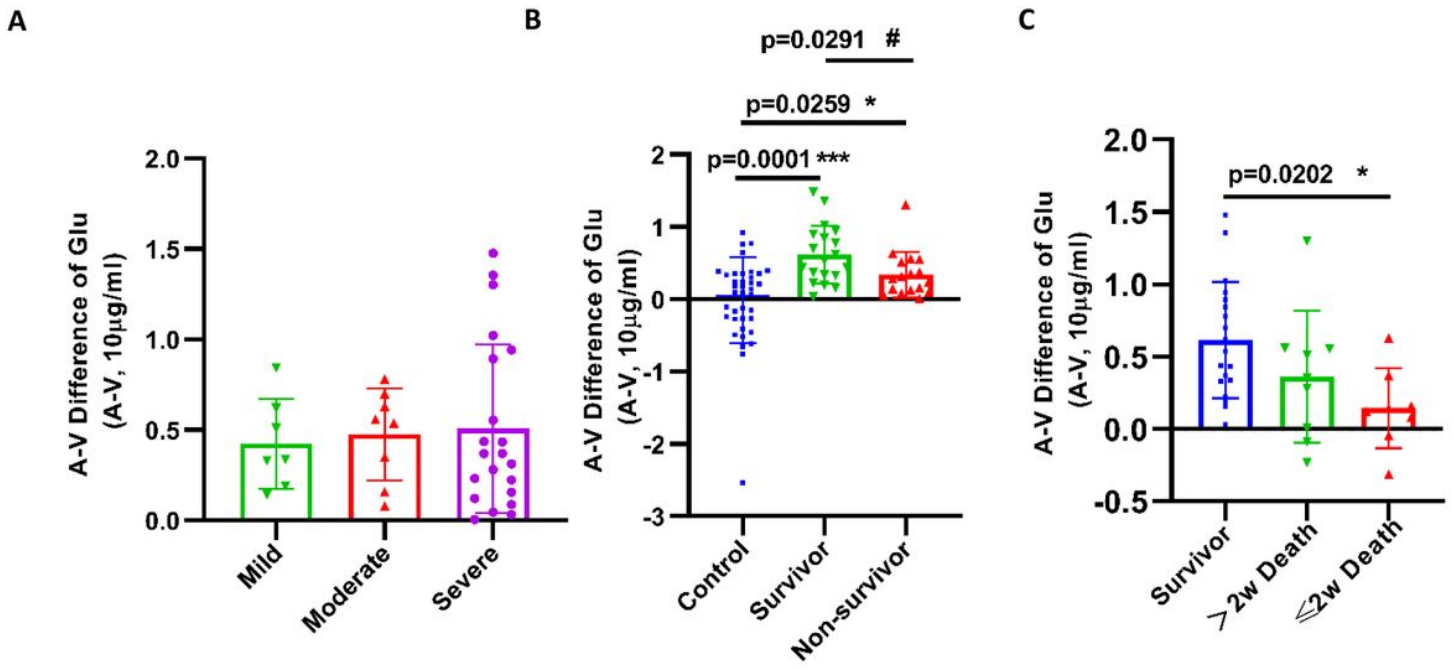

Figure 2

The association of Arterial-Venous differences (A-V) of Glu with ARDS severity and outcome. A) The association of Arterial-Venous differences (A-V) of Glu with ARDS severity; B) The association of Arterial-Venous differences (A-V) of Glu with patients final outcome; C) The association of Arterial-Venous differences (A-V) of Glu with patients live time after admission