Lung ultrasound score assessing the pulmonary edema in pediatric acute respiratory distress syndrome received continuous hemofiltration therapy: A prospective observational study

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Abstract

Background: Lung ultrasound score is a potential method for determining pulmonary edema in acute respiratory distress syndrome (ARDS). Continuous renal replacement therapy (CRRT) has become the preferred modality to manage fluid overload during ARDS. The aim of this study was to evaluate the value of lung ultrasound (LUS) score on assessing the effects of CRRT on pulmonary edema and pulmonary function in pediatric ARDS.

Methods: We conducted a prospective cohort study in 70 children with moderate to severe ARDS in a tertiary university pediatric intensive care unit from January 2016 to December 2018. 37 patients received CRRT (CRRT group) and 33 patients treated by conventional therapy (Non-CRRT group). LUS score was measured within 2 hours identified ARDS as the value of 1^{st} and the following three days as the 2^{nd}, 3^{rd}, and 4^{th}. We used *Spearman* correlation analysis to develop the relationship between LUS score and PaO_2/FiO_2, dynamic lung compliance (Cdyn), $PaCO_2$, oxygen index (OI), as well as between the change in daily fluid balance volume and the change in LUS score during CRRT.

Results: The 1^{st} lung ultrasound score in CRRT group were significantly higher than Non-CRRT group ($P < 0.001$), but the lung ultrasound score decreased gradually following CRRT ($P < 0.001$). LUS score was significantly correlated with PaO_2/FiO_2 (1^{st}: r=-0.800, 2^{nd}: r=-0.807, 3^{rd}: r=-0.703, 4^{th}: r=-0.584), Cdyn (1^{st}: r=-0.757, 2^{nd}: r=-0.906, 3^{rd}: r=-0.885, 4^{th}: r=-0.834), and OI (1^{st}: r=0.678, 2^{nd}: r=0.689, 3^{rd}: r=0.486, 4^{th}: r=0.324) based on 1^{st} to 4^{th} values (all $P<0.05$). LUS score decreased from 22 (18 - 25) to 15 (13 - 18) and PaO_2/FiO_2 promoted from 106.00 (96.00 - 121.50) mmHg to 160.00 (142.50 - 173.00) mmHg after CRRT for four days (both $P < 0.001$).

Conclusions: LUS score is significantly correlated with lung function parameters in pediatric ARDS. The improvement of pulmonary edema in patient with ARDS received CRRT can be assessed by the LUS score.

Background

Acute respiratory distress syndrome (ARDS) is characterized by a diffuse inflammatory condition of the lungs, decreased respiratory system compliance, bilateral pulmonary infiltrates and rapid onset of hypoxemic respiratory failure. The hospital mortality of ARDS was still high range from 35% to 46%, according to the report from the LUNG-SAFE study in a convenience sample of 459 in intensive care unit (ICU) from 50 countries(1). Pulmonary edema is one of the main forms of presentation caused by non-cardiogenic factors such as shock, sepsis, pneumonia, and other in ARDS(2). Reduction of pulmonary edema is critical for improving pulmonary function, and assessment of pulmonary edema is effective method in monitoring and guidance of therapy in patients with ARDS.

Though lung computed tomography (CT) is the gold standard for noninvasive evaluation of pulmonary edema, it is unsuitable to perform repeatedly in children with severe ARDS due to its radioactive hazard and safety(3). During ARDS, lung injury leads to increase the pulmonary capillary permeability and extravascular lung water (EVLW) resulting in pulmonary edema, which reflect the severity of the disease(4). Monitoring EVLW with pulse indicator continuous cardiac output ($PiCCO_2$) device is available at the bedside for estimating the physiologic correlated to pulmonary edema. However, accumulated evidences demonstrated that an association of EVLW and PaO_2/FiO_2 or oxygenation index (OI)(5) ([FiO_2×mean airway pressure (Paw)×100]/PaO_2) is affected by body weight (BW), height, or positive end-expiratory pressure (PEEP)(6-9). Moreover, detection of EVLW by a $PiCCO_2$ device is invasive and inconvenient. So, the relationship between EVLW and the PaO_2/FiO_2 ratio has been described as weak. Otherwise, lung ultrasound (LUS) could determine nearly all of pulmonary pathologic abnormalities such as pulmonary edema, consolidation, pneumothorax, pleural effusion. Recent reports indicated that LUS score is used as an alternative method for accurately evaluating pulmonary edema in ARDS (10, 11), and LUS score could assess EVLW (12) and oxygenation response to prone position ventilation in ARDS in adults (13). However, there is no report about the relationship between LUS score and pulmonary function in children with ARDS.

Patients with ARDS are usually complicated by acute kidney injury (AKI) and fluid overload. Renal replacement therapy (RRT) or continuous renal replacement therapy (CRRT) is an important adjuvant therapy for renal support, by maintaining hemodynamic stable and removing pro-inflammatory cytokines (14-18). Our previous study and other report indicated that patients with ARDS received RRT/CRRT had better outcome than that without CRRT (19, 20). Until now, there is little information.

Methods

Patients

A prospective cohort study was conducted, and children with moderate to severe ARDS admitted to pediatric intensive care unit (PICU) were enrolled from November 2016 to October 2019 at Shanghai Children's Hospital. Moderate to severe ARDS was defined according to the Berlin definition of ARDS (15). The exclusion criteria included: 1) patients who were in PICU less than 72 hours; 2) patients with lack of appropriate acoustic window; 3) patients with pneumothorax; 4) patients with hypoxemia secondary to cardiac disease congenital cardiovascular disease or chronic cardiopulmonary disease. According to whether CRRT were used during PICU stay, patients were divided into CRRT group and Non-CRRT group.

All the patients were received the mechanical ventilation based on lung protective-ventilation strategy or/and prone positioning, neuromuscular blockade (NMB), conservative fluid management (17). The total fluid volume was generally 60-70ml/kg.d or 1200-1500ml/m^2.d, blood transfusion if hemoglobin level down to 7.0g/dL during PICU stay (16). Patients received diuretics according to daily fluid balance when patients didn't receive CRRT.

The study protocol was approved by the local ethics committee of Children's Hospital affiliated to Shanghai Jiao Tong university (Approval number:2016R007-E03). The informed consent was signed by the patients' parents or relatives.

Lung ultrasound score

LUS was performed using a 13-6 MHz transducer (M-Turbo Ultrasound System, Mini-Dock-M Series, SonoSite). According to previous studies (18-21), patients were examined in supine, lateral, and prone positions applying the probe perpendicularly to the chest wall surface in order to get the longitudinal scan. Each hemithorax is divided into three regions by sternum, anterior and posterior axillary lines, and each region is divided into upper and lower halves. Each region should be correctly identified the pleura lines and A line by the linear probe in longitudinal scan.

Twelve areas are identified in turn and each region is assigned scores from 0 to 3. The LUS score is the sum of twelve areas, and the final LUS ranges from 0 to 36. In the present study, the definition of LUS score (22) and the representative images for different scores were shown (Table 1). The pathophysiological changes were described with different ultrasonic signs (23). All of the images and clips were collected and evaluated by two PICU expert physicians independently who had been trained and could complete lung ultrasound skillfully. All of the images, physical characteristics, baseline data and treatment of patients were all anonymizated when they were evaluated by these operators.

CRRT and mechanical ventilation

The CRRT mode was continuous veno-venous hemofiltration (CVVH) using Prismed or Prismaflex M60/100 membrane hemofilter equipped with an AN69 (Gambro Renal Products, Meyzieu, France) in a multifiltrate continuous renal replacement therapy machine (Gambro or Gambro prismaflex, Gambro Lundia Monitor Division, Lund, Sweden). The indications, performance, and management for CRRT were described as our previous study (14).

The modality of mechanical ventilation was intermittent mandatory ventilation (IMV) with PEEP levels 8-15cmH_2O and positive inspiration pressure (PIP) based on target tidal volume (Vt) of 4-8ml/kg (16). Parameters were aligned with lung protective ventilation strategy when patients met the diagnosis of moderate to severe pediatric ARDS.

Data collection

Demographic data such as age, sex, and body mass index (BMI), the pediatric risk mortality III (PRISM III) score(24) and co-morbidity were collected on PICU admission. Clinical parameters including fractional concentration of oxygen in inspired gas (FiO_2), PaO_2/FiO_2, $PaCO_2$, OI, dynamic lung compliance (Cdyn) which was continuously displayed using ventilators (MAQUET company, Servo-i serious) (25, 26) and daily fluid balance information, hospital mortality were collected. LUS score was determined within 2 hours after moderate to severe ARDS diagnosed as the value of 1^{st}, then measured every morning in following three days as the values of 2^{nd}, 3^{rd}, and 4^{th}. The schematic diagram of LUS score determination was shown in Figure 4. In addition, duration of mechanical ventilation, duration of CRRT, length of PICU or hospital stay was recorded.

Statistical Analysis

The data were performed with SPSS 17.0 statistics (SPSS Inc, Chicago). The characteristics of the patients were reported as percentages for categorical variables and compared the differences between groups by *chi*-square test. The continuous data with abnormal distribution were expressed as median (interquartile range, IQR) and compared using the Mann-Whitney *U* test. The correlation between LUS score and PaO_2/FiO_2, Cdyn, $PaCO_2$, OI and the correlation between the change in daily fluid balance volume and the change in LUS score during CRRT were all performed using *Spearman* correlation analysis. Friedman test was used to compare mean of more than 2 sets of data. *P* value < 0.05 was considered to be statistically significant.

Results

Baseline characteristics of patients

A total of 125 children with moderate to severe ARDS admitted to PICU were eligible from November 2016 to October 2019. Among them, there were 14 cases with less than 72h in PICU, and 6 patients were lack of appropriate acoustic window, 14 cases were pneumothorax and 21 patients were hypoxemia secondary to cardiac disease congenital cardiovascular disease or chronic cardiopulmonary disease. Finally, 70 children were enrolled in this study (Figure 1). The median age was 33 (10 - 52) months and 41 cases were male (58.57 %). The hospital mortality rate was 38.57 % (27/70). There were 37 patients in the CRRT group, and 33 patients in the None-CRRT group. The baseline characteristics and outcome of patients were summarized in Table 2. The PRISM III score, proportion of complication with AKI, OI, mechanical ventilation duration, length of PICU stay in the CRRT group were significantly higher than that in the Non-CRRT group ($P < 0.05$, Table 2), while PaO_2/FiO_2 was significantly lower in the CRRT group than the Non-CRRT group ($P < 0.001$, Table 2). There were no significant differences in age, gender, BMI, $PaCO_2$ and hospital mortality (all P 0.05, Table 2).

Correlation of LUS score to PaO_2/FiO_2, OI, $PaCO_2$, dynamic lung compliance and fluid balance

LUS score was negatively correlated with PaO_2/FiO_2 [1^{st}: $r = -0.800$, 2^{nd}: $r = -0.807$, 3^{rd}: $r = -0.703$, 4^{th}: $r = -0.584$, all $P < 0.001$] and dynamic lung compliance (Cdyn) [1^{st}: $r = -0.757$, 2^{nd}: $r = -0.906$, 3^{rd}: $r = -0.885$, 4^{th}: $r = -0.834$, all $P < 0.001$] based on 1^{st} to 4^{th} values after ARDS diagnosed. Positive relationships were observed between LUS score and OI [1^{st}: $r = 0.678$, 2^{nd}: $r = 0.689$, 3^{rd}: $r = 0.486$, 4^{th}: $r = 0.324$, all $P < 0.05$] during the first four days after ARDS diagnosed. The change in daily fluid balance volume was positively correlated with the change in LUS score during CRRT (the first day of CRRT: r=0.657, $P < 0.001$; the second day of CRRT: r=0.573, $P < 0.001$) (Figure 2).

The median of LUS score, PaO_2/FiO_2, OI, Cdyn in the CRRT group were significantly different during the first four days after identified ARDS (all $P < 0.001$, Table 3). CRRT group displayed peak median value of LUS score, OI, and the lowest median value of PaO_2/FiO_2, Cdyn one day after diagnosis as ARDS.

Thirty-six patients received CRRT on the second day after diagnosis (97.30%). In the Non-CRRT group, there were only significant difference in $PaCO_2$ during the first four days (P<0.001, Table 3).

Though the median of LUS score and OI in the CRRT group were higher than the Non-CRRT group during the first four days, but on the 4th day the difference between two groups decreased. The paired analysis revealed that PaO_2/FiO_2 in the CRRT group were significantly lower than that in the Non-CRRT group in first three days after diagnosis as ARDS (P≤0.001, Table 3). In the CRRT group, the PaO_2/FiO_2 and Cdyn increased after received CRRT and compared to Non-CRRT group, there were no significant difference between two groups on the 4th day (Figure 3). The representative images of LUS were presented as Figure 5.

The interval time between identified moderate to severe ARDS and CRRT initiation was 6.0 (3.0 - 10.5) hours, and the median duration of CRRT was 49.5 (45.0 - 53.5) hours. The median of LUS score [22 (18 - 25) *vs.* 15 (13 - 18)], PaO_2/FiO_2 [106.00 (96.00 - 121.50) mmHg *vs.* 160.0 (142.50 - 173.00) mmHg], OI [15.92 (14.07 - 17.73) *vs.* 9.49 (8.70 - 10.58)], and Cdyn [0.40 (0.30 - 0.42) ml/cmH_2O/kg *vs.* 0.60 (0.51 - 0.65) ml/cmH_2O/kg] were determined at initiation and after CRRT target weaned in the CRRT group. These results indicated that LUS score and OI after CRRT weaned were significantly lower, and PaO_2/FiO_2 and Cdyn were increased (P≤0.001, Table 4). Otherwise, only the value of $PaCO_2$ was decreased on the 4th day after ARDS diagnosis in the Non-CRRT group (P = 0.006, Table 4).

Discussion

In this study, we found that LUS score is correlated with PaO_2/FiO_2, Cdyn, OI in pediatric ARDS, and the changes of LUS score are associated with the improvement of fluid balance and pulmonary function by CRRT intervention in pediatric ARDS.

Lung ultrasound is a convenient and repeatable approach used in critically ill patient's bedside nowadays. In the last decade, a meta-analysis showed that lung ultrasound had a high sensitivity and specificity in critically ill patients who were characterized by pulmonary pathology (27), especially in aspect of assessing EVLW (28, 29). The association of EVLW determined by $PiCCO_2$ with PaO_2/FiO_2 or OI is affected by BW, height, or PEEP (6-9). According to previous report, LUS as a convenient, noninvasive and portable technique could detect various pathophysiological changes including lung edema and derecruited lung (20, 21, 30), and LUS can detect the increased EVLW by the appearance of B-lines in ARDS (31). It is worth noting that LUS score is correlated with PaO_2/FiO_2, OI, and Cdyn during the first four days after ARDS diagnosis in the present study. The data in our study provides support for the suggestion that LUS score could be a way to quantify the oxygenation state, compliance of lung and the requirement of ventilation pressure in pediatric ARDS. LUS score might more sensitive and specific for assessing pulmonary function compared with invasive determination of EVLW by $PiCCO_2$. Moreover, B-lines increased and could be detected despite a normal PaO_2/FiO_2 ratio in animal model of lung injury (32), suggesting that LUS score is an early indicator for assessing pulmonary function. Furthermore, the child's thorax is smaller and the chest wall is thinner. So, the visualization of pulmonary ultrasound in longitudinal scan is better than that of adults. To our knowledge, this is the first report about the LUS score as a potential tool for EVLW measurement in estimating pulmonary function in a large pediatric population with ARDS.

It is well known that fluid overload and AKI were the mainly indications for CRRT intervention in patients with ARDS (33). Our previous multi-center prospective study found that CRRT could significantly decrease hospital mortality rate in pediatric ARDS secondary to sepsis (14). The pathophysiology of ARDS is inflammatory storm caused by various insults leads to capillary leak and increased EVLW. According to the standard care of patients with moderate to severe ARDS, the use of hemofiltration might be potential tool for negative fluid balance, which is associated with improved lung function (34). To date, it is lack of effective tool to accurately evaluate the effects of hemofiltration on pulmonary edema and pulmonary function. LUS score has been proposed for semi-quantification of lung aeration (22). In our study, all the daily median of LUS score after diagnosed as ARDS in the CRRT group were higher than these in the Non-CRRT group and CRRT group had peak median value of LUS score on one day after diagnosis as ARDS. More importantly, a significant reduction in LUS score disappeared following CRRT, and LUS score were positively correlated with the change in daily fluid balance volume in the CRRT group. All these results implied that CRRT improves pulmonary function partially contributed by improvement of pulmonary edema, which might relate to fluid balance by CRRT. As far as we know, this is first report about the closely relationship between LUS score and the effects of CRRT on pulmonary function.

There are several limitations to be considered. First, our study included in a single PICU and baseline characteristics were different between CRRT and Non-CRRT group, which affected the power of the conclusion. Second, due to its limitation of invasiveness, the relationship between the value of EVLW determined by $PiCCO_2$ and LUS score was not analyzed. Third, the finding of that LUS score may be provide a threshold value for the initiation of CRRT in pediatric ARDS would need to be validated in more detailed and larger studies. Nevertheless, the results give a new insight into the benefits from monitoring LUS score to assess the severity and the effect of CRRT on pulmonary function in pediatric ARDS.

Conclusions

LUS score, as an alternative indicator for pulmonary function, is closely correlated to PaO_2/FiO_2, OI and Cdyn in pediatric ARDS. The improvement of CRRT on pulmonary function can be assessed by the LUS score. As an easily repeatable, noninvasive, and quantitative tool for detecting pulmonary edema and other pathological signs, the value of LUS score is worth further investigation in a large pediatric population.

Abbreviations

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; CT: computed tomography; EVLW: extravascular lung water; OI: oxygenation index; BW: body weight; PEEP: positive end-expiratory pressure; LUS: lung ultrasound; AKI: acute kidney injury; RRT: renal replacement therapy; CRRT: continuous renal

replacement therapy; PICU: pediatric intensive care unit; NMB: neuromuscular blockade; CVVH: continuous veno-venous hemofiltration; IMV: intermittent mandatory ventilation; PIP: positive inspiration pressure; Vt: tidal volume; BMI: body mass index; PRISM III: pediatric risk mortality III; FiO_2: fractional concentration of oxygen in inspired gas; Cdyn: dynamic lung compliance.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the local ethics committee and conducted in accordance with the ethical standards laid down in the Declaration of Helsinki (Ethics Committee of Children's Hospital affiliated to Shanghai Jiao Tong university [Approval number:2016R007-E03]). The informed consent was signed by the patients' parents or relatives.

Consent for publication: Consent for publication has been obtained from all persons for the included images.

Availability of data and materials: All data generated or analysed during this study are included in this published article (and its supplementary information files).

Competing interests: All of the authors declare that they have no competing interests.

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Authors' contributions: YZ2 was responsible for conceptualization and supervised the whole process. FW and CW were responsible for data curation, formal analysis and wrote the manuscript. JS, YS, HM, TS and YZ1 were responsible for data curation and drafting part of the initial manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Definition of LUS score and representative images in this study.

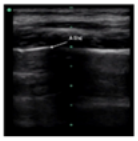
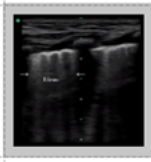
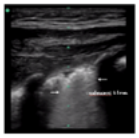
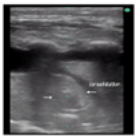
LUS score	Definition	Representative image
0	A lines （less than 3 B lines）	
1	more than 3 well-spaced B lines	
2	coalescent B lines	
3	consolidation	

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Table 2. Baseline characteristics and outcome of patients with moderate to severe acute respiratory distress syndrome in this study.

Characteristics	Non-CRRT (n = 33)	CRRT (n= 37)	*P- value*
Age, month	24 (9-53)	35 (12-52)	0.667
Male, n (%)	19 (57.58)	22 (59.46)	0.873
PRISM	15 (12-18)	17 (15- 20)	0.016
BMI	14.70 (12.65-16.86)	14.00 (12.70-16.38)	0.778
Co-morbidity, n (%)			
Immune system disease	1 (3.03)	4 (10.81)	0.207
Genetic metabolic disease	1 (3.03)	0 (0)	0.286
Leukemia/Tumor	6 (18.18)	7 (18.92)	0.937
Complication, n (%)			
Hepatic failure	2 (6.06)	1 (2.70)	0.489
AKI	9 (27.27)	25 (67.57)	0.001
Brain dysfunction	1(3.03)	1(2.70)	0.935
Gastrointestinal dysfunction	2(6.06)	3(8.11)	0.740
pancreatitis	0(0)	2(5.41)	0.175
PaO_2/FiO_2, mmHg	163.00 (142.50-175.00)	123.00 (110.50-138.50)	< 0.001
OI	7.69（6.46- 9.50）	13.15（10.00- 14.78）	< 0.001
$PaCO_2$, mmHg	55.00 (38.00- 61.00)	45.00 (34.50-62.00)	0.225
Duration of mechanical ventilation, day	6 (4-9)	8 (6-15)	0.012
Length of PICU stay, d	10 (6-17)	14 (10-20)	0.047
Length of hospital stay, d	19 (12-30)	24 (17-35)	0.081
Hospital mortality, n (%)	11 (33.33)	16 (43.24)	0.395

Table 3. LUS score, respiratory dynamics in with (CRRT) and without hemofiltration (Non-CRRT) group.

Parameters	CRRT (n= 37)					Non-CRRT (n= 33)				
	1	2	3	4	*P*	1	2	3	4	*P*
LUS	18(16-20)[a]	22(18-25)[a]	18(16-22)[a]	14(12-18)[b]	0.000	14(12-16)	14(12-16)	14(10-17)	12(9-16)	0.154
PaO_2/FiO_2, mmHg	123.50(111.00-139.25)[a]	105.00(91.00-121.00)[a]	127.00(109.00-148.00)[a]	160.00(142.50-170.50)	0.000	163.00(142.50-175.00)	152.10(143.00-179.00)	160.00(140.00-183.00)	165.00(136.50-192.50)	0.395
OI	13.15(10.00-14.78)[a]	15.85(13.54-17.46)[a]	11.63(10.24-14.47)[a]	9.47(8.63-10.50)[b]	0.000	7.69(6.46-9.50)	8.84(8.25-10.18)	8.60(7.56-11.05)	8.12(6.85-10.45)	0.242
$PaCO_2$, mmHg	45(35-62)	42(38-50)	40(38-45)[b]	40(38-45)	0.078	55(38-61)	46(41-52)	45(40-50)	42(38-45)	0.006
Cdyn, $ml/cmH_2O/kg$	0.38(0.31-0.58)[a]	0.40(0.30-0.42)[a]	0.44(0.38-0.56)[a]	0.60(0.51-0.66)	0.000	0.61(0.46-0.72)	0.61(0.50-0.71)	0.60(0.44-0.68)	0.63(0.45-0.70)	0.315
PEEP	12(12-14)[a]	14(13-15)[a]	12(11-14)[a]	10(9-11)[a]	0.000	9(7-10)	9(8-10)	9(8-11)	8(8-10)	0.032

[a] $P<0.001$ for CRRT group vs. Non-CRRT group; [b] $P<0.05$ for CRRT group vs. Non-CRRT group.

Table 4. LUS score, respiratory dynamics in with (CRRT) and without hemofiltration (Non-CRRT) group.

	CRRT (n= 37)			Non-CRRT (n= 33)		
	Pre-CRRT	Post-CRRT	*P*	1st day	4th day	*P*
LUS	22 (18-25)	15 (13-18)	<0.001	14 (12-16)	12 (9-16)	0.154
PaO_2/FiO_2, mmHg	106.00 (96.00-121.50)	160.00 (142.50-173.00)	<0.001	163.00 (142.50-175.00)	165.00 (136.50-192.50)	0.395
OI	15.92 (14.07-17.73)	9.49 (8.70-10.58)	<0.001	7.69 (6.46-9.50)	8.12 (6.85-10.45)	0.242
$PaCO_2$, mmHg	41 (38-50)	40 (38-45)	0.102	55 (38-61)	42 (38-45)	0.006
Cdyn, $ml/cmH_2O/kg$	0.40 (0.30-0.42)	0.60 (0.51-0.65)	<0.001	0.61 (0.46-0.72)	0.63 (0.45-0.70)	0.315

Figures

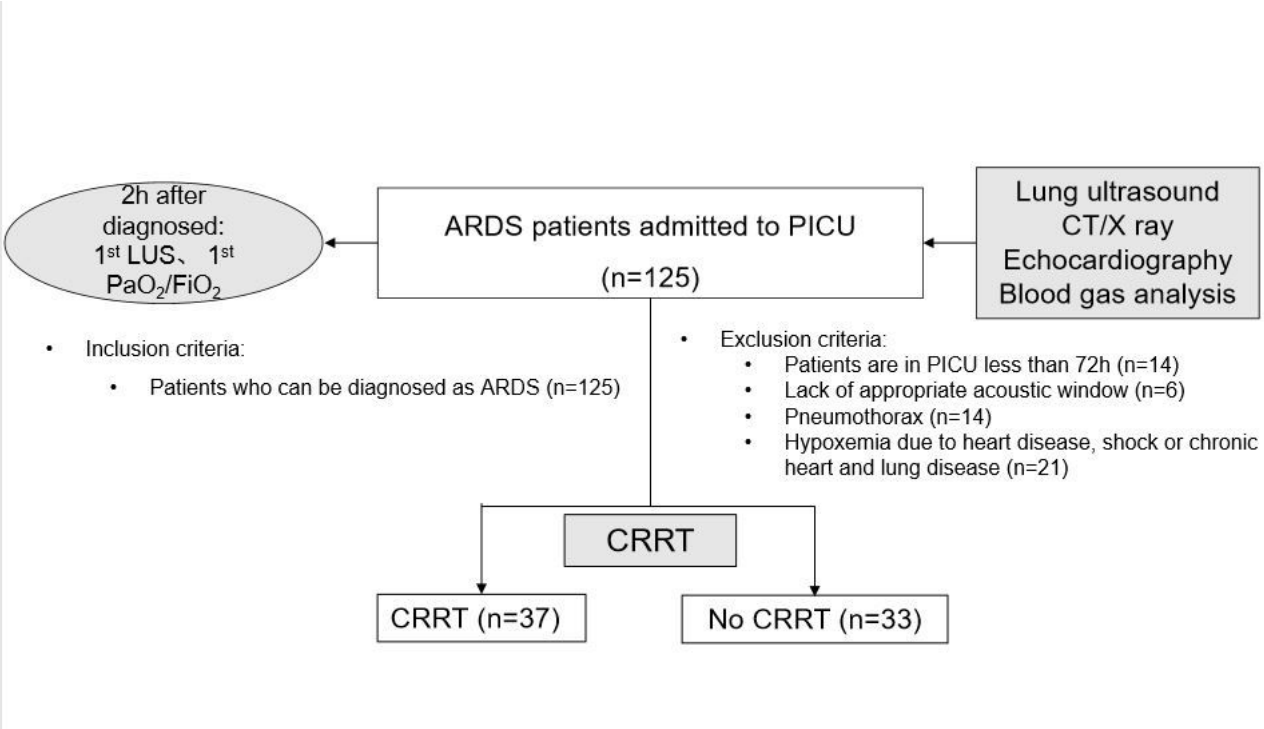

Figure 1

Flowchart for patients' enrollment.

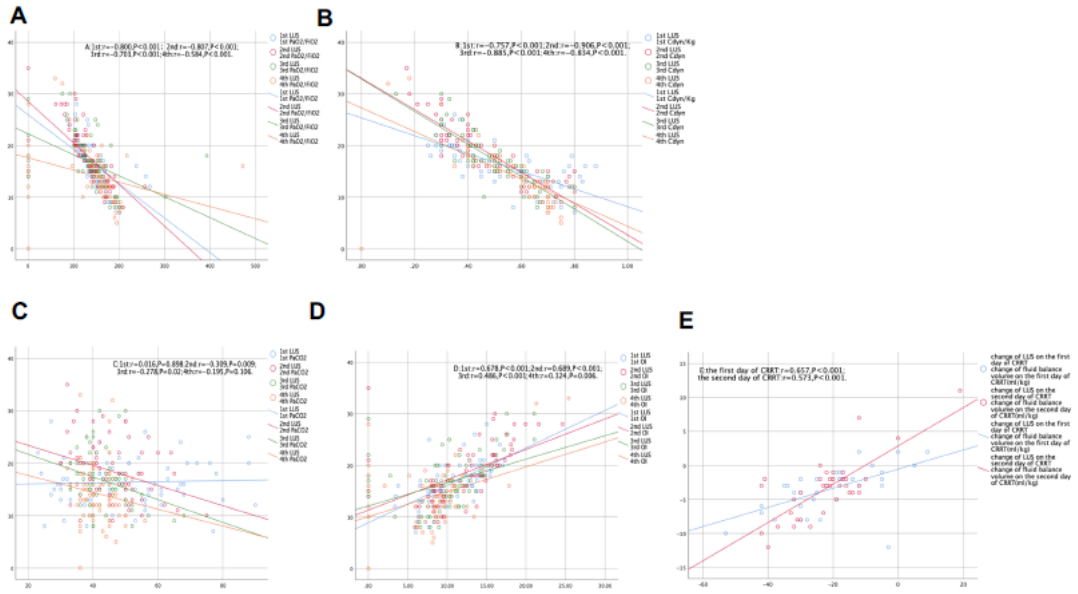

Figure 2

Scatterplots demonstrating the correlation between LUS score and respiratory dynamics in ARDS.

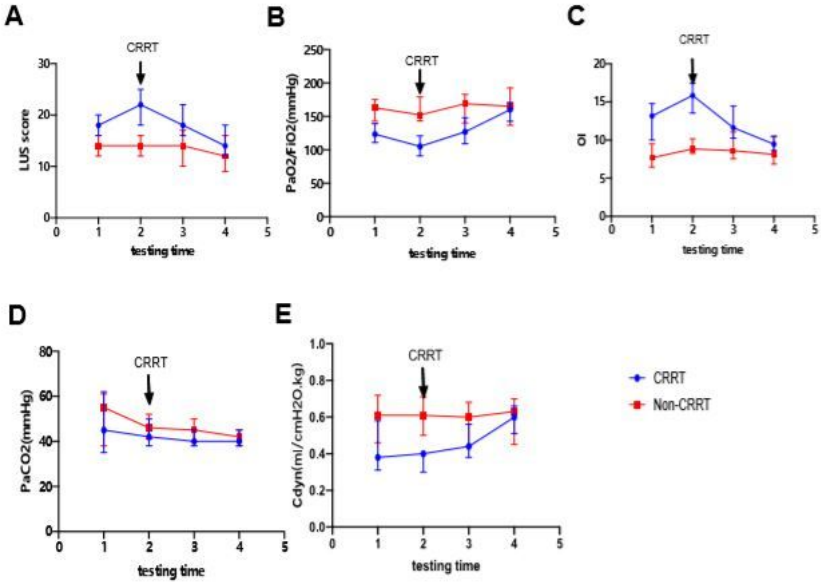

Figure 3

Comparison of LUS score, respiratory dynamics in with (CRRT) and without hemofiltration (Non-CRRT) group.

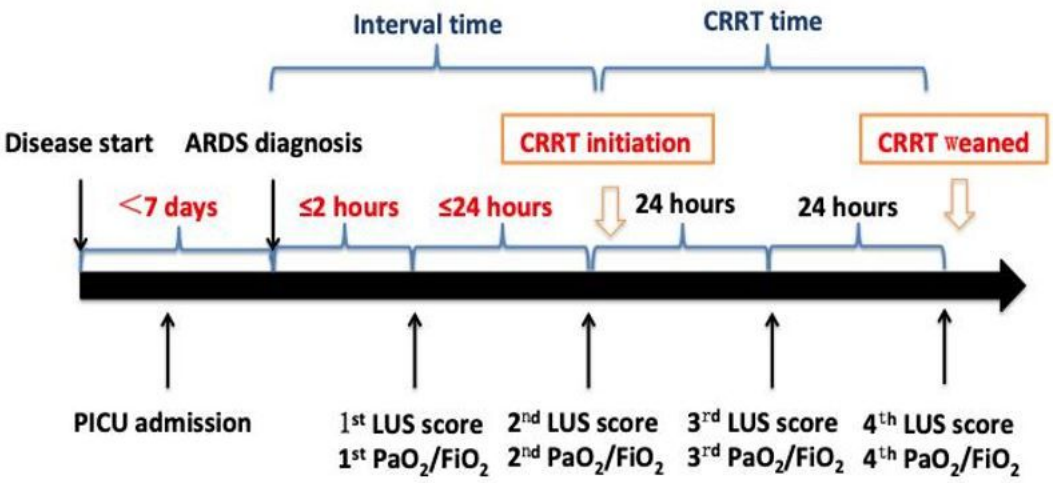

Figure 4

The schematic diagram of LUS score determination.

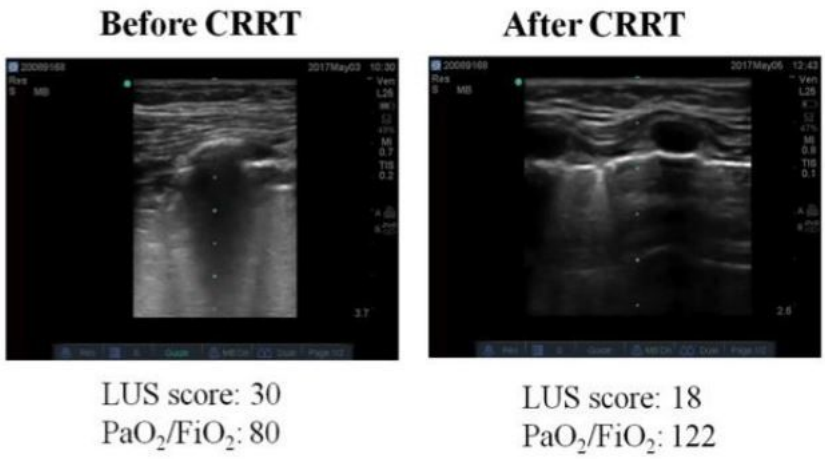

Figure 5

The representative images of LUS before and after hemofiltration.

Supplementary Files

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- CONSORTChecklist.doc