

A Modificatory Screening Protocol for ARDS in Patients with Respiratory Support Based on SpO₂ and FiO₂

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A Modificatory Screening Protocol for ARDS in Patients with Respiratory Support Based on SpO₂ and FiO₂

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Abstract

Background: A large number of recent studies have confirmed that the pulse oximetric saturation (SpO₂)/fraction of inspired oxygen (FiO₂) ratio (SFR) correlate well with PaO₂/FiO₂ ratio (PFR). However, whether SFR can replace PFR for the diagnosis and evaluate the severity of ARDS patients with advanced respiratory support is unclearly. The purpose of this study is to explore potential value of SFR ratio as a new diagnostic tool for ARDS by establishing new processes in patients who require high levels of oxygen support.

Methods: 341 patients were included in this study, SFR and PFR values were recorded in the same time. 161 patients were used to establish the model, and 180 patients were used to verify the validity of the model. 161 groups of data were divide into hypoxic group (group H) and non-hypoxic group (group N) according to whether SpO₂ was greater than 97%. For group H, the regression equation was established to describe the relationship between SFR and PFR. and calculated the value of SFR when PFR is 300. For group N, the correlation between each observation data and PFR were analyzed. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic value of the index. Finally, a new diagnostic process was established for ARDS based on these results, and the reliability was verified with Berlin definition set as the gold standard for diagnosis and classification.

Results: For group H, the diagnostic linear equation is $PFR = 0.9162 * SFR - 21.39$ ($R^2=0.66$, $P<0.0001$). After calculation, when PFR is 300, SFR is 352. For group N, There is a significant negative correlation between FiO₂ and PFR($R= -0.521, P<0.0001$). The AUC of using FiO₂ to diagnose ARDS was 0.694 (95%CI 0.571~0.817, $P < 0.005$). When the cutoff value of FiO₂ was 39%, the sensitivity was 0.838 and the specificity was 0.545. Therefore, in this new diagnosis progress, when $SpO_2 \leq 97\%$, if $SFR \leq 352$, ARDS may exist; when $SpO_2 > 97\%$, if $FiO_{2min} > 39\%$, there may be ARDS. The sensitivity, specificity, NPV, PPV, and accuracy of the new diagnosis progress for ARDS were 91.1%, 76.7%, 89.6%, 79.6%, and 83.9%, respectively.

Conclusion: There are potential value of SpO₂ and FiO₂ as a noninvasive diagnostic tool for ARDS by new processes in patients who are already receiving high levels of oxygen support.

Keywords: ARDS; PaO₂/fraction of inspired oxygen ratio; SpO₂/fraction of inspired oxygen ratio; FiO₂;Diagnose

KEY POINTS

Question: Is there any potential value of SpO₂ and FiO₂ as a diagnostic tool for ARDS Early Noninvasive Screening Protocol ?

Findings: In this new diagnosis progress, when SpO₂≤97%, if SFR≤352, ARDS may exist; when SpO₂>97%, if FiO₂min>39%, there may be ARDS. The sensitivity, specificity, NPV, PPV, and accuracy of the new diagnosis progress for ARDS were 91.1%, 76.7%, 89.6%, 79.6%, and 83.9%.

Meaning: There are potential value of SpO₂ and FiO₂ as a noninvasive diagnostic tool for ARDS. Continuous monitor SpO₂ and FiO₂ could enable clinicians to recognize ARDS timely and accurately.

Background

Acute respiratory distress syndrome (ARDS) is devastating clinical syndromes with associated mortality more than 40%^[1], which can be caused by a variety of etiologies. Although ARDS is a common fatal disease, In the LUNG SAFE study, the largest international cohort of patients with ARDS, however, there were two-thirds of patients who were delayed or missed the diagnosis of ARDS^[2]. In the absence of accurate identification of ARDS, effective treatments have not been fully applied, including protective mechanical ventilation, fluid restriction, and prone positioning. PFR is the center of understanding, describing, and treating ARDS. PFR is not only used in the definition of ARDS, but also used to grade the severity of ARDS^[3].

In the absence of significant progress in the recognition and treatment of ARDS, an arterial blood gas analysis is required to determine the PFR of a patient, but patients who are not suspected of having ARDS may not undergo ABG examination, and frequent blood gas monitoring are also questioned. In addition, Bellani et al^[4]. confirmed that even though the PFR is reached the standard, clinicians still could not recognize ARDS timely, due to ABG testing is too rare and discontinuous in one day, and parts of ARDS patients with contraindications of arterial puncture or in institutions without blood gas analysis conditions. Therefore, the development of approaches to enable more timely recognition has the potential to save lives.

In 2016, Riviello and his colleagues^[5] proposed that an SFR less than or equal to 315 can be used as the oxygenation standard under resource constraints, which is known as Kigali modification, and has been widely used. Brown et al.^[6, 7] used the method of non-linear calculation to obtain accurate PFR in ARDS patients based on the SFR. However, the inclusion criteria for SpO₂ in this study was less than 96%. But, the patients who use ventilator or oxygen therapy to maintain SpO₂ ≤ 96% may face with an early lung injury. If ignored, it may cause the disease to worsen^[4]. At the same time, It is difficult to identify ARDS early when SpO₂ > 96% in patients with

non-pulmonary causes of oxygen therapy. In particular, high flow oxygen therapy (HFNO) is currently widely used as an effective therapeutic support for acute respiratory failure in patients with ARDS, such as COVID-19^[8, 9]. Studies have shown that the clinicians should focus on the severity of patients with lung injury to require high levels of oxygen support, suggesting the concept that the diagnosis of ARDS should not depend on the presence of an endotracheal tube or positive-pressure ventilation in adults^[10]. Recently, Matthay et al^[11] recommend that the Berlin definition of ARDS be broadened to include patients treated with HFNO of at least 30 L/min who fulfil the other criteria for the Berlin definition of ARDS and propose that this would be an advance for patients with lung injury who require high levels of oxygen support. In this case, from an epidemiological perspective, the inclusion of these patients would more comprehensively identify those with ARDS at an earlier stage of the syndrome, and would include more patients in resource-limited settings, as was recommended with the Kigali modification of the Berlin definition of ARDS. Therefore, the purpose of this study is to explore potential value of SFR ratio as a new diagnostic tool for ARDS again by establishing new processes in patients who require high levels of oxygen support.

Methods

Study Design and Study Population

This study is a prospective observational studies, and was conducted in Yijishan Hospital Affiliated to Wannan Medical College. The study was approved by the First Affiliated Hospital of Wannan Medical College and participating institution ethics committees (approval number: 2019-97). This is an observational study, arterial blood samples and vital signs monitoring are parts of its standard treatment. The requirement for written informed consent was waived by the IRB. This clinical trial was registered in Chinese Clinical Trial Registry (ChiCTR, ChiCTR2000029217) by Weihua Lu in 19 January 2020, which was prior to patient enrollment.

The inclusion criteria is that patients who are admitted to the Department of Critical Care Medicine in our hospital from August to October 2020 and require arterial blood gas analysis and ECG monitoring due to their condition. Patients with contraindications to arterial puncture, methemoglobinemia and other reasons that affect data collection are excluded. All the arterial blood samples were analyzed using the blood gas analyzer (Danish Raydu ABL800 FLEX) within one minute after the blood collection, and the monitor (China Mindray iPM-12) was used to record the SpO₂ and vital signs data immediately after the blood collection. To ensure the accuracy of the data, the blood oxygen saturation sensor is placed on a clean thumb; the blood oxygen saturation waveform is stable; there is no posture change or sputum suction operation at least 10 minutes before the measurement.

Data Collection

Demographic and clinical data of the included patients were collected: gender, age, etc. Immediate percutaneous peripheral blood oxygen saturation (SpO₂), inspired oxygen concentration (FiO₂), arterial oxygen partial pressure (PaO₂), respiratory rate (RR) were recorded, SpO₂/FiO₂ ratio (SFR) and PaO₂/FiO₂ ratio (PFR) values were calculated according to the above information.

Statistical Analysis

All normal distribution measurement data are represented by ($\bar{x} \pm s$), non-normal distribution count data are represented by median (P25, P75), and count data are represented by example(%). The two independent sample t test was used for the comparison between the normal distribution measurement data, the Mann-Whitney U test was used for the comparison between the nonnormal distribution measurement data, and the χ^2 test was used for the comparison between the count data. The test level is two-sided $\alpha=0.05$, $P<0.05$, which indicates that the difference is statistically significant.

Establishment of the New Diagnosis Tool: 341 patients were included in this study, SFR and PFR values recorded in the same time. 161 patients were used to establish the model, and 180 patients were used to verify the validity of the model. 161 groups of data were divide into hypoxic group (group H) and non-hypoxic group (group N) according to whether SpO₂ was greater than 97%. For group H, the regression equation was established to describe the relationship between SFR and PFR. and calculated the value of SFR when PFR is 300. For group N, the correlation between each observation data and PFR were analyzed and choose the value index. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic value of the index. Finally, use SFR and the index to establish a new diagnostic process for ARDS. After determining the new diagnostic process, the Berlin definition is used as the gold standard to calculate the NPV, PPV, accuracy, sensitivity and specificity of the new diagnostic method.

Verify the Reliability of the New Diagnosis Tool: At the same time, another group of 180 ICU patients requiring blood gas analysis were collected to verify the reliability of the diagnosis tool. The Berlin definition is used as the gold standard to diagnose the presence or absence of ARDS. According to the Berlin definition grading standard, the corresponding SFR values were calculated with PFR of 100, 200 and 300 as the cutoff values, and the accuracy of the new method used for grading was verified.

Results

Of the 375 patients who needed arterial blood gas analysis in the Department of Intensive Care Medicine of our hospital , 34 were excluded due to their inaccurate data collection. Finally, there were 341 patients included in this study, including 160 males (46.9%) and 181 females (53.1%). The subjects were randomly divided into two cohort(**Fig 1**). The basic information of the research objects is shown in **Table 1**.

Establishment of a New Diagnosis Process

1. Linear equations of group H

1.1 The correlation between SFR and PFR Finally, there are 87 cases in group H. because the data is not normally distributed, Spearman correlation is used to evaluate the correlation between SFR and PFR. SFR and SFR have a strong positive correlation ($R^2=0.66, P < 0.001$).

1.2 Establishment of Linear Regression

To further clarify the correlation between SFR and PFR. The Linear regression between SFR and PFR was performed. linear regression equation indicated that there is a strong linear relationship between SFR and PFR ($R^2=0.66, P < 0.0001$). the linear regression equation as follows:

$$PFR = 0.9162 * SFR - 21.39$$

The linear relationship diagram is shown in **Fig 2**.

2. The correlation between FiO₂ and PFR in group N There are 74 cases in group N. All the SpO₂ more than 97%. correlation analysis shows than only the FiO₂ and PFR have a significant negative correlation ($R = -0.521, P < 0.0001$). The receiver operation characteristic curve (ROC curve) was used to investigate the value of FiO₂ in diagnosis of ARDS, The AUC of using FiO₂ to diagnose ARDS was 0.694 (95%CI 0.571~0.817, $P < 0.005$). the best cutoff value of FiO₂ was 39%, the sensitivity was 0.838 and the specificity was 0.545. The ROC curve is shown in **Fig 3**.

3. Establish a New Diagnosis Tool Based on the above results, we set up a new diagnosis process as follows (**Fig 4**): when a patients with suspicious ARDS, the SpO₂ ≤ 97%, calculate SFR according to the formula: $SFR = SpO_2 / FiO_2$, if $SFR \leq 352$, ARDS may exist. When SpO₂ > 97%, if high concentration inhaled oxygen is required, ie FiO_{2min} > 39%, ARDS may exist.

Reliability of the New Diagnostic Method

A total of 180 patients in the intensive care medicine department of our hospital who needed arterial blood gas analysis due to their condition were included in the verification group, There are both 90 cases with $SpO_2 \leq 97\%$ and $SpO_2 > 97\%$. With the Berlin definition as the gold standard, the sensitivity, specificity, NPV, PPV, and accuracy of the new diagnostic tool were 91.1%, 76.7%, 89.6%, 79.6%, and 83.9%.

The utility of different SFR cutoffs for ARDS prediction

According to the established linear regression equation ($PFR = 0.9162 * SFR - 21.39$), when PFR is 300, SFR is 352, when PFR is 200, SFR is 241, and when PFR is 100, SFR is 132. ROC curves were used to investigate the value of different SFR cut-off value in diagnosis of ARDS, The 3 presented cutoffs demonstrated good specificity (98.5%, 62.8%, and 93.1%, respectively) and sensitivity (61.1%, 89.2%, and 63.4%, respectively). And the PPV and NPV were also high. The utility of the new method for ARDS classification was verified in **Table 2**.

Discussion

Our study reinforce the value of using SpO_2 and FiO_2 as an noninvasive diagnostic tool for ARDS, We also set up a new diagnosis process base on SpO_2 and FiO_2 , when a patients suspicious with ARDS, the $SpO_2 \leq 97\%$, calculate SFR according to the formula: $SFR = SpO_2 / FiO_2$, if $SFR \leq 352$, ARDS may exist; when $SpO_2 > 97\%$, if high concentration inhaled oxygen is required, ie $FiO_{2min} > 39\%$, ARDS may exist. Meanwhile, We verified the accuracy of the model, The model has a very high sensitivity and specificity. Our finding could to enable clinicians to recognize ARDS timely and accurately, especially in developing countries which lacking sufficient medical resources. However, saturation-based measurements are easily available in relatively resource-poor settings.

The establishment of the Berlin definition in 2012 made the diagnosis and classification of ARDS more accurate and standardized^[12]. However, repeated blood draws in the ICU environment may lead to iatrogenic anemia, the need for blood transfusions, an increased risk of infection, and an increase in hospital costs^[13]. In addition, as mentioned earlier, many underdeveloped regions and countries may lack the conditions for arterial blood gas. Therefore, a large number of recent studies^[6, 14, 15] have confirmed that SFR can be used to evaluate ARDS patients. For example, Kigali University Teaching Hospital proposed that if arterial blood gas and chest X-ray are difficult to achieve, SpO₂/FiO₂ ratio and lung ultrasound Can be used as a substitute for diagnosis of ARDS^[16].

This study confirmed that there is a strong correlation between SFR and PFR, and it is statistically significant ($r=0.873$, $P<0.0001$), which means that this non-invasive methods can be used to estimate PaO₂ and oxygenation index in clinical work. This is similar to the results of Katherine DesPrez, BA^[14]. They proposed that SFR can be used as a substitute for PFR and provide noninvasively prognostic information and assess the severity of ARDS. The linear regression equation of the relationship between SFR and PFR calculated in this study is $PFR = 0.9162 * SFR - 21.39$, which has a higher correlation coefficient, which shows that the formula in this study may be more in line with the linear relationship between SFR and PFR. The oxygenation index calculated by this formula may be more accurate. When SpO₂>97%, statistical analysis shows that FiO₂ is significantly correlated with PFR($R = -0.521, P < 0.0001$). In clinical applications, if the blood oxygen saturation is within the normal range due to the excessively high inspired oxygen concentration, there maybe ARDS too^[17].

In the oxygen dissociation curve^[18], it can be seen that the curve drawn by the arterial blood oxygen saturation with the change of the arterial blood oxygen partial pressure is divided into three sections: upper, middle and lower. In the middle and lower part of the curve, the curve is steep, and SaO₂ changes greatly with PaO₂, which is conducive to hemoglobin releasing oxygen for tissue utilization. Therefore, separating

the data with $SpO_2 \leq 96\%$ for linear regression, the correlation between the two is higher than before. In the upper part, the curve is flat, and SaO_2 changes little with PaO_2 . Therefore, when $SpO_2 > 97\%$, the PFR calculated by the linear formula is not accurate. Through statistical analysis, there is a significant correlation between FiO_2 and PFR at this time. when FiO_2 more than 39%. The sensitivity of using FiO_2 to diagnose ARDS is high, which is conducive to the early warning of ARDS. In the early research of Rice TW et al.^[19], they also explored the relationship between SpO_2 and PaO_2 and concluded that it is similar to this experiment, but they only analyzed the data of $SpO_2 \leq 97\%$. They pointed out in the discussion that in the oxygen dissociation curve, the slope of SpO_2 and PaO_2 in the saturated state is almost zero, and a large change in PaO_2 may cause little or no change in SpO_2 . So it excludes patients' data with high oxygen saturation. However, in clinical work, patients who rely on high concentration oxygen support, even though the monitor indicates that the blood oxygen saturation is normal, they may already have ARDS^[20]. In this case, if they are not detected and treated early, which may cause illness deterioration. In our research, if the minimum FiO_2 ($SpO_2 > 97\%$) is greater than 39%, the patient may have early ARDS. The results of this study are of great significance to avoid ignoring the occurrence and development of ARDS. On the basis of the research results, a flow chart was drawn for the rapid diagnosis tool of high-risk patients (Fig3). Taking Berlin's definition as the gold standard for diagnosis, the diagnosis of the new diagnostic process has high sensitivity and specificity, indicating that the new diagnostic tool is suitable for early recognition of ARDS. However, a large sample of multiple centers is still needed for further verification.

However, it is worth mentioning that not all patients are suitable for condition assessment using this method. For example, in the case of carbon monoxide poisoning, peripheral circulatory failure, etc., it may not be possible to use finger pulse oxygen to monitor blood oxygen saturation, and blood gas analysis is the only way to rule out this disease^[21]. Transcutaneous blood oxygen saturation technology transmits two wavelengths of light (usually 660nm and 940nm) through the tissue to measure the

absorbance change of each wavelength over time. The absorption of light by the tissue is cyclic, which is due to the circulation of the heart and the resulting pulsation of arterial blood into the tissue bed. However, COHb and O₂Hb have similar absorption characteristics at 660nm. Therefore, the percutaneous oxygen saturation (SpO₂) of patients with carb monoxide and peripheral circulatory failure must not be an accurate measurement of O₂Hb^[22]. A recent observational study also confirmed that in patients using VV-ECMO, transcutaneous oxygen saturation is a poor oxygenation test. Due to the increase in COHb levels, as the VV-ECMO support time increases, Its reliability is reduced^[23]. This situation can also be seen in long-term smokers. Early studies have confirmed that the COHb content in the blood of long-term smokers will increase by 15%^[24]. Recent study has shown that carboxyhemoglobin saturation (SpCO) baseline levels are significantly higher in long-term smokers than in nonsmokers^[25]. Under these above circumstances, only blood gas analysis and percutaneous carbon monoxide analyzer can judge the patient's true oxygenation situation comprehensively.

Moreover , the new procedures should not obscure the need to exclude left heart failure or primary lung disease (such as autoimmune disease or acute eosinophilic pneumonia). The expanded definition will enable the diagnosis of ARDS to be more widely applicable and will help identify patients in the early stages of the syndrome as well as patients with severe clinical lung injury who are already receiving high levels of oxygen support. The implementation may improve patient clinical practice and clinical outcomes.

There are some shortcomings in this study. First of all, it is a single-center observational study with a small sample size, so the new diagnostic tool needs to be verified by a multi-center large-sample study. In addition, we explored the linear relationship between SFR and PFR without considering the influence of other factors on the oxygen dissociation curve, such as pH, CO₂, etc.. This is because the purpose of this study is to explore the general relationship between the two, so that diagnostic

tools can be used even when these confounders are unknown. Similarly, we did not conduct separate studies on different ventilation modes, such as ventilation mode and PEEF, etc.. Finally, this study only verified the efficacy of this new diagnostic tool, and did not explore its correlation with the prognosis of ARDS patients, which could be explored in later studies.

Conclusions

Measurement of the SpO_2 and FiO_2 performed as well as PaO_2 in diagnosis of ARDS and grade the severity, while avoiding invasive arterial blood gas monitoring. Meanwhile, Continuous monitor SpO_2 and FiO_2 could enable clinicians to recognize ARDS timely and accurately, especially for patients with lung injury who require high levels of oxygen support.

Abbreviations

ARDS=acute respiratory distress syndrome; SFR= SpO₂/fraction of inspired oxygen ratio; PFR=PaO₂/fraction of inspired oxygen ratio; ROC=Receiver operating characteristic;AUC=Area Under Curve; ABG=Arterial blood gas; ICU=Intensive Care Unite.

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Disclosures

Name: Weihua Lu, MD

Contribution: This author was responsible for the conceptualization of the study and the revision and approval of this manuscript.

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Contribution: These authors were participated in the design and drafted the manuscript.

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Contribution: These authors collected data and were responsible for its accuracy.

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Contribution:These authors helped to revise the manuscript.

All authors contributed to the data analysis and interpretation. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the First Affiliated Hospital of Wannan Medical College and participating institution ethics committees (approval number: 2019-97).

Trail registration

ChiCTR. ChiCTR2000029217. Registered in 19 January 2020,
<http://www.chictr.org.cn/showproj.aspx?proj=43364>

Consent for publication

All authors have approved the manuscript and its publication.

Competing interests

The authors have no competing interests.

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Table 1. Characteristics of subjects

Characteristics	n=341
Sex, n (%)	
Male	160 (46.9)
Female	181 (53.1)
Mean body weight (range), kg	57 ± 10.11
Age (range), years old	48(19-78)
Mean FiO ₂ (range), %	45.7 (20-100)
Mean PaO ₂ (range), mmHg	93.84 (35.4-230)
Mean SpO ₂ (range), %	94.82 (63-100)
Mean PFR (range)	226.57 (48.9-540)
Mean SFR (range)	226.40 (73.8-456)

Table 2. Utility of SFR for ARDS classification (SpO₂ ≤ 97%)

SFR	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	+LR,-LR
<132	61.1	98.5	84.6	95	40.73 ^a ,0.39
<241	89.2	62.8	74.2	83	2.39,0.17
<352	63.4	93.1	82.5	83.3	9.18,0.04 ^b

^a:The likelihood of diagnosing ARDS is significantly increased when the positive likelihood ratio is greater than 10. ^b:The likelihood of excluding ARDS is significantly increased when the negative likelihood ratio is less than 0.1.

Figures

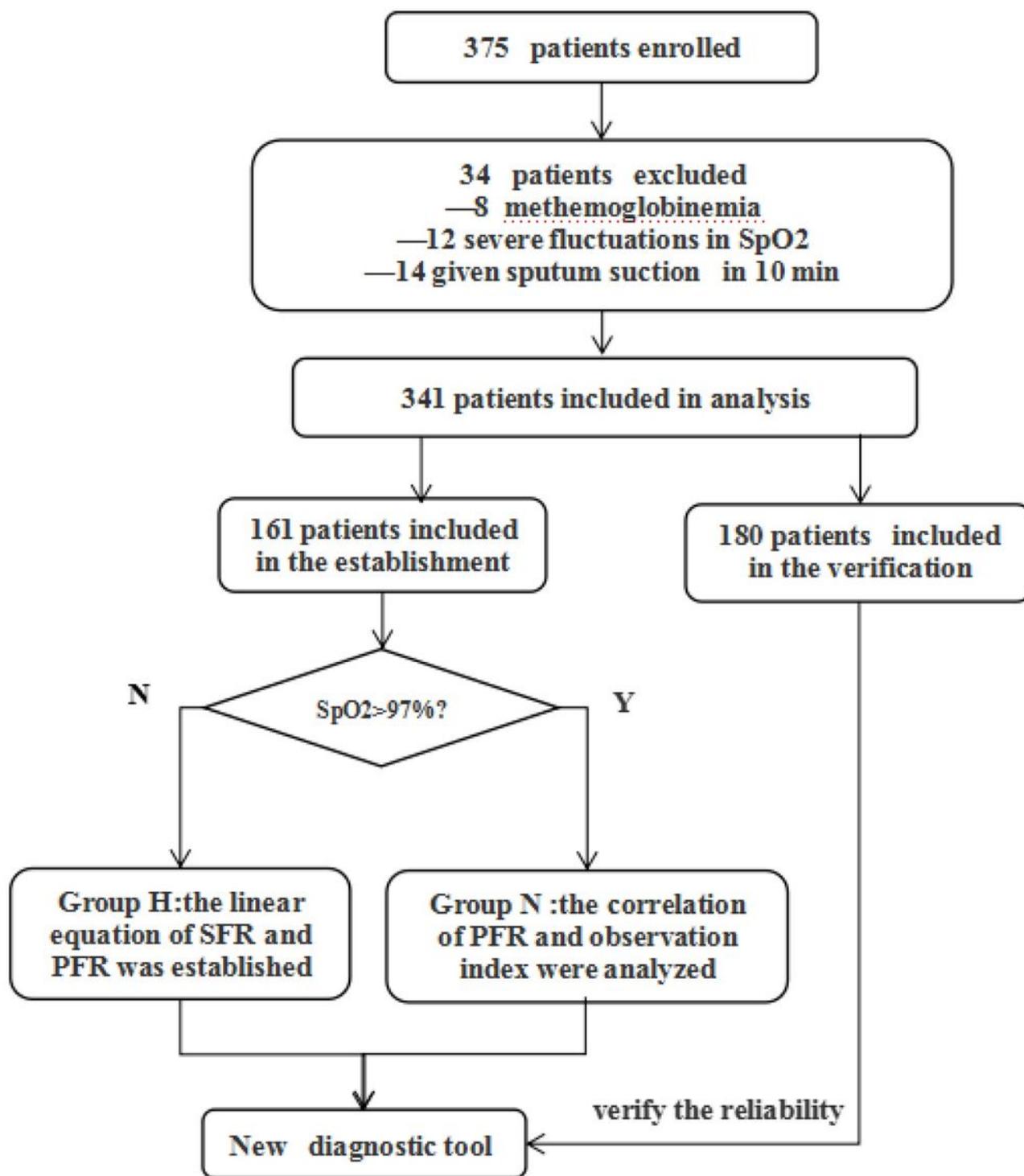


Figure 1

Finally, there were 341 patients included in this study, including 160 males (46.9%) and 181 females (53.1%). The subjects were randomly divided into two cohort(Fig 1)

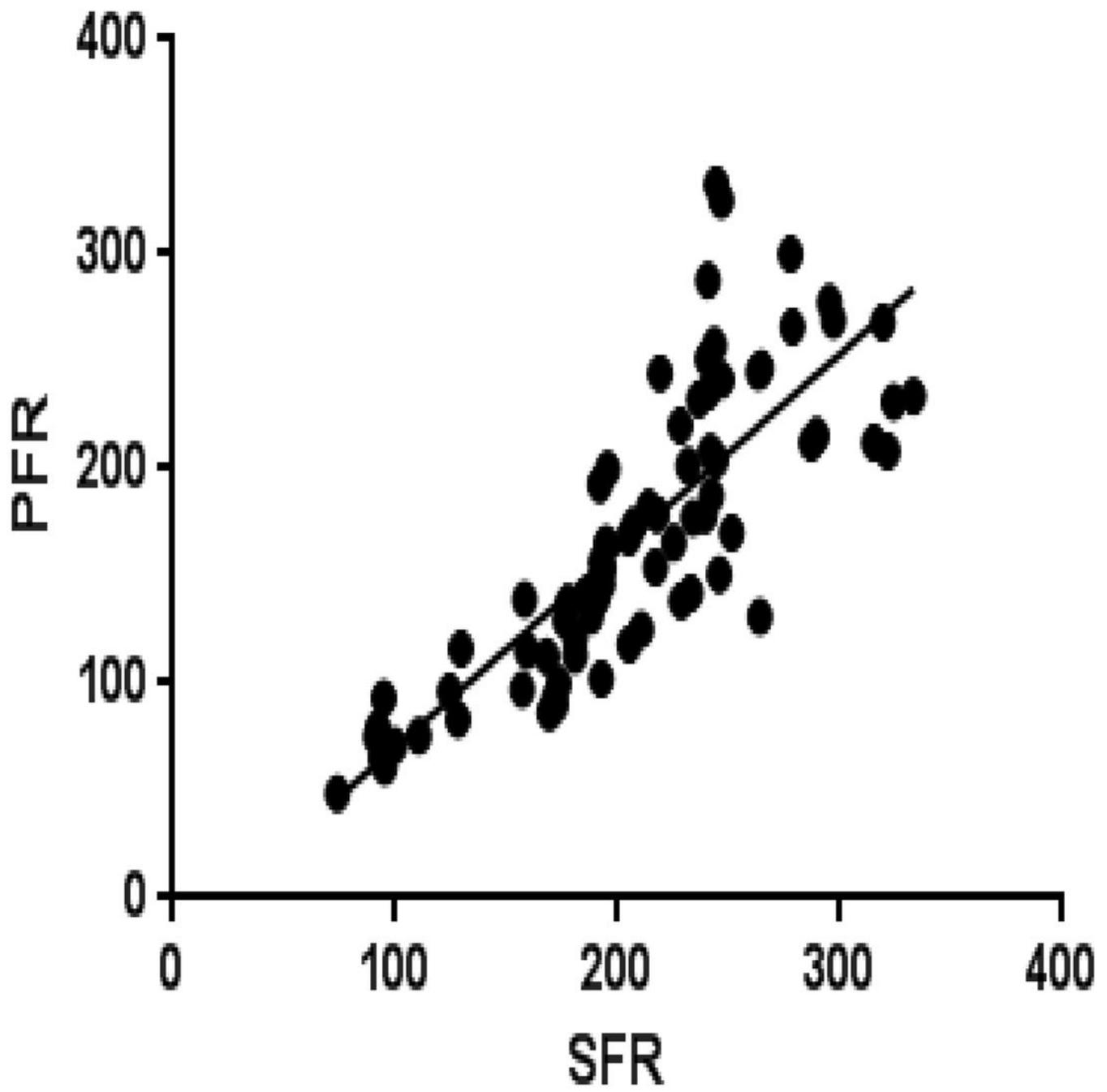


Figure 2

The linear relationship diagram is shown in Fig 2.

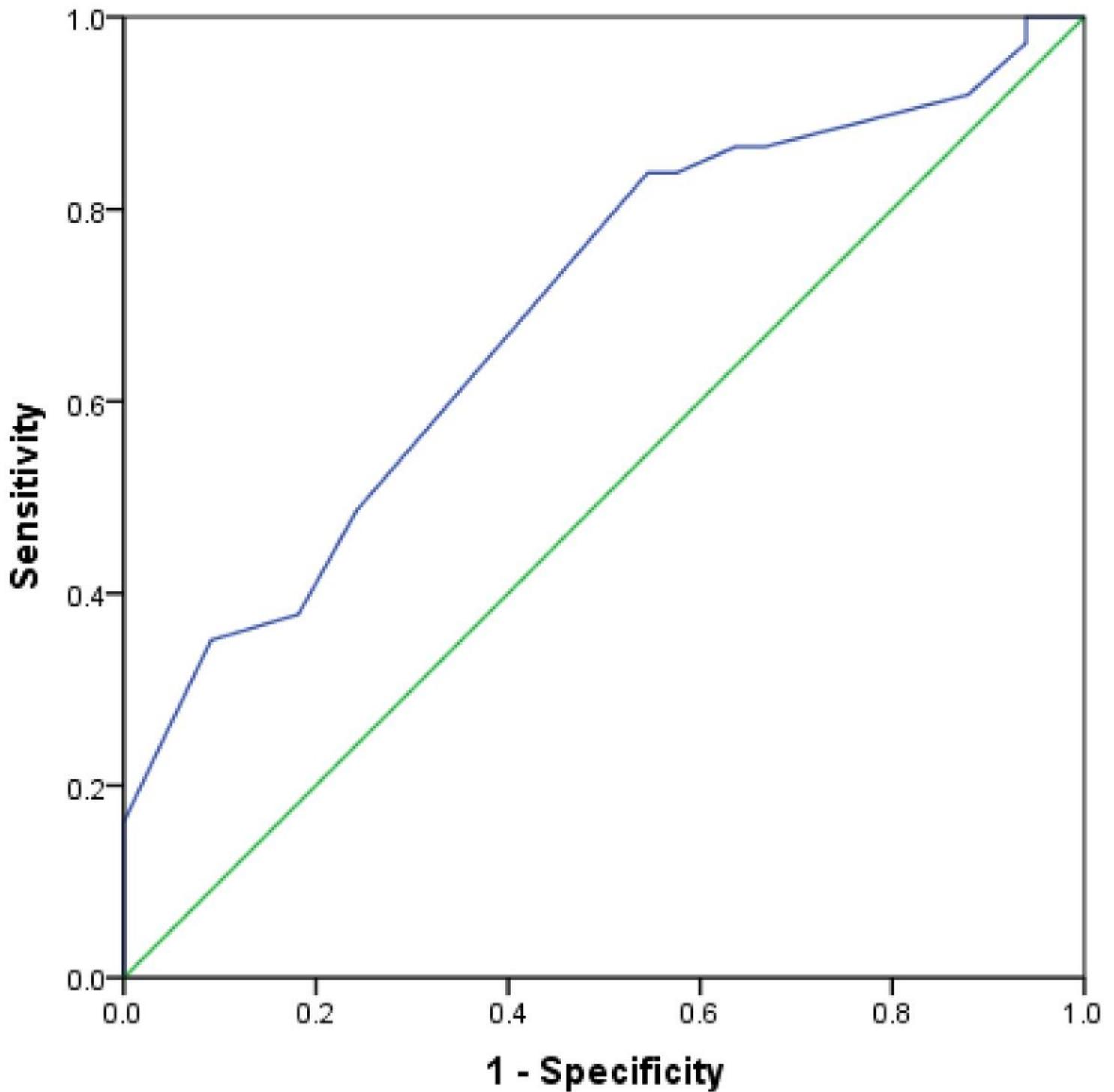


Figure 3

the best cutoff value of FiO₂ was 39%, the sensitivity was 0.838 and the specificity was 0.545. The ROC curve is shown in Fig 3.

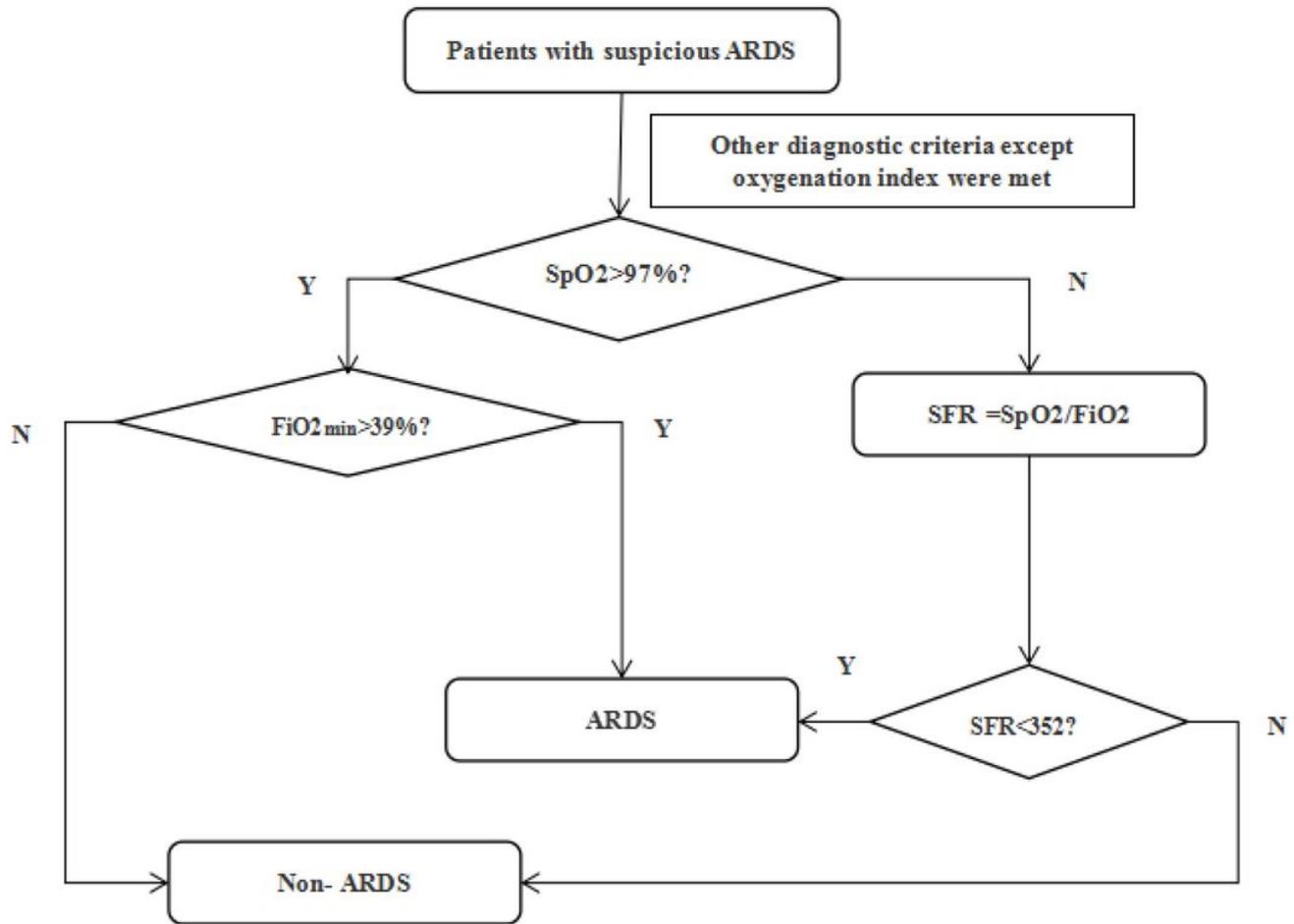


Figure 4

Based on the above results, we set up a new diagnosis process as follows (Fig 4)

Supplementary Files

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

- [STARDchecklist.docx](#)