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Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-861102/v1>

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Assessment of Non-linear Imputation of PaO₂/FiO₂ from SpO₂/FiO₂ Among Patients receiving Mechanical Ventilation in China

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Abstract

Objectives: Arterial blood gas measurements are not always immediately available despite their potential relevance to management of mechanically ventilated patients. Retrospective and prospective studies have validated the non-linear imputation of PaO₂/FIO₂ from SpO₂/FIO₂, predominantly in USA. In this study, the objective was to validate the non-linear imputation algorithm among mechanically ventilated patients in the Chinese population.

Method: Mechanically ventilated patients admitted to the emergency departments or ICUs at two participating hospitals in China were enrolled prospectively. At the time of a clinical arterial blood gas being drawn, SpO₂, oximeter waveform characteristics, receipt of vasopressor, and skin pigmentation were simultaneously recorded. For the various imputation methods, we calculated both imputation error and the area under the curve for patients meeting criteria for acute respiratory distress syndrome (PaO₂/FIO₂ ≤ 300) and moderate-severe acute respiratory distress syndrome (PaO₂/FIO₂ ≤ 150).

Result: We studied 663 arterial blood gases from 646 patients; 177 (26%) arterial blood gases were associated with SpO₂ less than or equal to 96%. Non-linear imputation had lower mean absolute error than linear imputation method when SpO₂ was less than or equal to 96% (p<0.001). At the PaO₂/FiO₂ threshold of 300 or less, non-linear imputation AUC (0.90 95% CI 0.85-0.95) was not significantly higher than the AUCs of linear and log-linear imputation methods (0.88 95% CI 0.82-0.94). The same result was shown at the PaO₂ /FiO₂ threshold of 150 or less. For patients with a threshold SpO₂ of 96% or less, AUC analysis yielded similar results between non-linear vs. linear and log-linear imputations.

Conclusions: In this cohort of mechanically ventilated patients, non-linear imputation was not superior to linear and log-linear imputations for patients with SpO₂ of 96% or less. All strategies performed similarly in estimating PaO₂/FIO₂ from SpO₂/FIO₂.

Key Words: sequential organ failure assessment; pulse oximetry; acute respiratory distress syndrome; severity scores

Introduction

The ratio of PaO₂/FIO₂ is used to evaluate the respiratory function with respect to the severity of hypoxemia and is a component to the Berlin Criteria for acute respiratory distress syndrome (ARDS) [1, 2]. To calculate the PaO₂/FiO₂ ratio, arterial blood gas (ABG) measurement is usually obtained [3]. However, mechanically ventilated patients may not have ABG measurement readily available at relevant timepoints. Lack of accurate knowledge of the degree of hypoxemia can lead to delayed recognition and treatment of patient with ARDS [4]. Pulse oximetry is routinely available and provides a continuous monitoring of oxyhemoglobin percent saturation (SpO₂) in the blood stream [5]. Prior studies of the relationship between SpO₂ and PaO₂ in adults have shown it to be a reliable noninvasive surrogate for calculating PaO₂ and ultimately the PaO₂/FiO₂ ratio used for diagnosing ARDS [6, 7].

It is known that skin pigmentation and sensor type can affect SpO₂ readings, thus affecting the accuracy of imputed PaO₂ values [8]. Previous studies on predominantly Caucasian cohorts have shown that non-linear imputation of PaO₂ from SpO₂ outperforms linear and log-linear imputations [6, 7]. We hypothesized that non-linear imputation is more accurate than the linear or log-linear methods in a Chinese cohort.

Methods

The study was approved by the Institutional Review Board at each study site and was registered at ClinicalTrials.gov with Identifier: NCT02598492 (<https://clinicaltrials.gov/ct2/show/NCT02598492?term=02598492&draw=2&rank=1>). Registered 09-01-2015. Data were collected using electronic case report forms (CRFs) from two participating hospitals in China. Patients were admitted to the EDs or ICUs at participating hospitals. Non-intubated adults, children under the age of 18, pregnant women and prisoners were excluded from the study. ABG was obtained from patients along with body temperature, SpO₂, pulse oximeter type, make, model, location, and waveform. The pulse oximeters used in the study are part of the bedside monitoring equipment that come from four different companies: MINDRAY iPM 10, EDAN iM8, BIOLIGHT A5, and COMEN 8000F. Simultaneously, information whether the patient received vasopressors medications, such as epinephrine, norepinephrine, phenylephrine, dopamine, or vasopressin, were collected. Skin pigmentations from light to dark on a five- point scale was recorded at the time of ABG with reference pigmentation on the electronic CRFs (**Supplement 1**). Each patient was evaluated based on 2012 Berlin ARDS criteria: (1) acute onset within one week; (2) chest imaging shows bilateral opacities that cannot be fully explained by effusions, lobar/lung collapse, or nodules; (3) respiratory failure not fully explained by cardiac failure or fluid overload; (4) PaO₂/FiO₂ ratio [1]. Chest imaging were reviewed by the site investigators. SOFA score was calculated for each patient and recorded in the CRFs. Relevant data variables such as age, sex, height, weight, and blood chemistry (within 24 hours of ABG), were abstracted. Data were centralized and uploaded using REDCap.

The ABGs analysis was classified into all ABGs and ABGs with SpO₂ ≤ 96%. SpO₂ ≤ 96%'s imputation is considered the most accurate based on the hemoglobin-oxygen dissociative curve's sigmoidal shape and prior study [6, 7]. We used Ellis non-linear,

Rice linear, and Pandharipande log-linear equation for imputation (the equation displayed on the supplemental) [4, 9, 10]. The difference between measured and imputed PaO₂/FiO₂ as a function of measured PaO₂/FiO₂ was depicted with the Bland-Altman plot for both all the ABGs and the ABGs with SpO₂ ≤ 96%. To determine the proportion of the imputation error, we calculated the absolute error of the imputation that was less than 25 (i.e., if the actual PaO₂/FiO₂ was 100, then the imputed PaO₂/FiO₂ is between 75 to 125) and 50 (i.e., if the actual PaO₂/FiO₂ was 100, then the imputed PaO₂/FiO₂ is between 50 to 150). After bootstrapped the root mean squared error (RMSE) for each imputation technique, we compared it with paired t-test for hypothesis testing.

According to Brown et al., we also calculated the area under the receiving operating characteristic curve (AUC) at two diagnostic thresholds for PaO₂/FiO₂ (150 and 300) for each imputation technique [7]. The linear and the log-linear imputation have identical AUC because their imputation technique derived from SpO₂/FiO₂ to PaO₂/FiO₂, whereas the linear imputation technique imputed PaO₂ from SpO₂. We used the DeLong method to compare AUCs. Since PaO₂/FiO₂ is affected by other variables, we also used multivariable logistic regression to obtained AUC for both PaO₂/FiO₂ (150 and 300) thresholds [11]. We included variables that directly or indirectly affected the hemoglobin-oxygen dissociation curve, such as age, BMI; body temperature; serum pH; kidney function (markers for renal dysfunction, i.e., BUN, creatinine); and serum electrolytes (i.e., sodium, bicarbonate, chloride, and potassium); mechanical ventilator parameters (i.e., minute ventilation, PEEP, tidal volume per ideal body weight), and ABG parameters (i.e., ABG collection time, pulse oximeter waveform quality, ABG result). Analysis was performed in the R Statistical Package version 4.0.3 [12].

Results

We studied 663 ABGs in 646 patients across two participating hospitals in China, among which 177 ABGs were associated with SpO₂ less than or equal to 96%. Patient characteristics are displayed in **Table 1**. Characteristics of the ABG, associated oximetry measurements, relevant laboratory results and ventilator settings are displayed in **Table 2**. For skin pigmentation, 66% of patient's the skin pigmentation were light to medium, and 25% were medium. The mean measured PaO₂/FiO₂ ratio was 174. Mean PEEP was 5cm H₂O; mean tidal volume based on predicted body weight was 6±1mL/kg.

As displayed in **Figure 1**, Bland-Altman plots suggested that non-linear imputation had no superiority over linear or log-linear imputation, and all imputation methods showed an increasing accuracy at lower PaO₂/FiO₂ ratios, especially for measured PaO₂/FiO₂ ratio less than or equal to 150 and for SpO₂ less than or equal to 96%. In **Table 3**, we quantitatively compared the error of each imputation technique. For participants with SpO₂ less than or equal to 96%, non-linear imputation had lower mean absolute error than linear imputation method (p<0.001) but did not have lower mean absolute error than log-linear (P=0.218). For participants with SpO₂ less than or equal to 96% and ARDS, non-linear imputation had lower mean absolute error than linear imputation (p<0.001) and log-linear imputation (p=0.075).

As outlined in **Table 4**, no significant discrimination was displayed among the imputation methods. The area under receiver operating characteristic curve (AUC) of these methods ranged from 0.87 to 1 for different thresholds and subpopulations, suggesting all methods showed good to excellent sensitivity and specificity. The AUC between non-linear and linear/log-linear imputation methods were not significantly different in both thresholds (PF ratio < 150 and PF ratio $\leq$ 300) as the 95% confidence intervals overlapped substantially (ROC comparison for all imputation methods in **Supplement 2**). For patients whose SpO₂ was less than or equal to 96% threshold, AUC analysis yielded similar results between non-linear and linear/log-linear imputations which no imputation method was better.

Furthermore, we sought to improve the accuracy of the imputations by incorporating additional covariates in the AUC models (i.e., ABG variables, mechanical ventilation variables, pulse oximetry location and wave form, and others that mentioned in methods). However, the AUCs did not significantly improve (**Supplement 3**).

Discussion

Our study is the first to verify the accuracy of non-linear imputation, linear imputation, and log-linear imputation among mechanically ventilated patients in a Chinese population. We found that the non-linear imputation had lower mean absolute error than linear imputation method for ABGs when SpO₂ was less than or equal to 96%. Based on AUC analysis, at both PaO₂/FiO₂ threshold ($\leq$ 300 and $\leq$ 150) and for patients with SpO₂ $\leq$ 96%, the non-linear imputation AUC did not differ significantly than linear and log-linear imputation methods. Thus, we did not find evidence for superiority of the non-linear imputation method in a Chinese population in whom high SpO₂ was common.

There are limitations in our study. Although non-linear imputation showed lower mean absolute error for ABGs where SpO₂ was less than or equal to 96%, it did not show superiority over linear imputation and log-linear imputation in AUC analysis, which was not consistent with our prior retrospective and prospective observational studies. We analyzed the possible reasons for the inconsistency with prior results. First, samples in this study were gathered from only two hospitals, and the sample size of ABGs associated with SpO₂ less than or equal to 96% was less than 30 percent of all ABGs. Previous studies had greater than 60 with SpO₂ less than or equal to 96%, non-linear imputation showed less error than linear but not significantly different with log-linear imputations [6, 7]. Besides, the small sample diversity and magnitude also made the comparison between non-linear and linear/log-linear imputations at the PaO₂ /FiO₂ less than or equal to 300 and SpO₂ less than or equal to 96% threshold incommensurable. Second, most of the ABG samples were collected regularly at 5am, 2pm and 11pm, when doctors and nurses were on ward rounds, although the risk of bias is low. Third, the cohort in this study is homogenous but the pulse oximeter devices used in our study are not the same types as the ones in prior studies.

Conclusion

In a Chinese cohort of prospective paired measurement of ABG and SpO₂, non-linear imputation was not superior over linear imputation and log-linear imputation, and the imputation strategies perform well in estimating PaO₂ /FiO₂ from SpO₂/FiO₂.

Ethical Approval and Consent to participate

The study was approved by the Institutional Review Board at each study site and was registered at ClinicalTrials.gov with Identifier: NCT02598492 (<https://clinicaltrials.gov/ct2/show/NCT02598492?term=02598492&draw=2&rank=1>). Registered 09-01-2015.

Consent for publication

All authors approved the submitted version.

Availability of supporting data

Not applicable.

Competing interests

All authors declare no competing interests.

Funding

This project is sponsored by Brigham and Women's Hospital.

Authors' contributions

Peter C. Hou and Liga Yusvirazi conceived the study in consultation with all other authors; Shan Wang and Liga Yusvirazi had full access to all of the data and take responsibility for the content of the manuscript, including data and analysis. Liga Yusvirazi and Samuel M. Brown analyzed the data; Shan Wang and Liga Yusvirazi wrote the first draft; all authors reviewed and revised the manuscript for important intellectual content.

Acknowledgements

We thank the doctors, nurses and respiratory therapists at Guangzhou Red Cross Hospital, and First Medical Center of Chinese People's Liberation Army General Hospital who graciously participated in this work.

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Figures

Figure 1

Bland-Altman plot of the difference between measured and imputed Pao₂/Fio₂ (PF) ratios. Blue represents nonlinear, red represents linear, and green represents log-linear imputation results. ABG = arterial blood gas.

Supplementary Files

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- [Tablesfiguresandsupplement.pdf](#)