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

Shan Wang (swang344-c@my.cityu.edu.hk)  
City University of Hong Kong  
https://orcid.org/0000-0003-1614-3092

Liga Yusvirazi  
Kaiser Permanente

Haiyan Yin  
Jinan University First Affiliated Hospital

Hongjun Kang  
Chinese PLA General Hospital

Yan Zhao  
Chinese PLA General Hospital

Li Wang  
Chinese PLA General Hospital

Samuel M. Brown  
Intermountain Medical Center

Peter C. Hou  
Brigham and Women's Hospital

Research

Keywords: sequential organ failure assessment, pulse oximetry, acute respiratory distress syndrome, severity scores

Posted Date: September 13th, 2021

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

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Assessment of Non-linear Imputation of PaO2/FiO2 from SpO2/FiO2 Among Patients receiving Mechanical Ventilation in China

Shan Wang†, Liga Yusvirazi‡, Haiyan Yin§, Hongjun Kang¶, Yan Zhao‡, Li Wang‡, Samuel M. Brown§, Peter C. Hou∥

†: Department of Biomedical Engineering, City University of Hong Kong, Hong Kong, China.
‡: Department of Emergency Medicine Kaiser Permanente Central Valley, Modesto, California, USA.
§: Department of Intensive Care Unit, The First Affiliated Hospital of Jinan University, Guangzhou 510000, Guangdong, China.
¶: Department of Critical Care Medicine, First Medical Center of Chinese People’s Liberation Army General Hospital, Beijing 100853, China
§: Department of Internal Medicine, Intermountain Medical Center and University of Utah School of Medicine, Salt Lake City, Utah, USA
∥: Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA.

*Corresponding author: Shan Wang

Email: swang344-c@my.cityu.edu.hk

† Shan Wang and Liga Yusvirazi contributed equally to this work.
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, BIONLIGHT A5, and COMEN 8000F. Simultaneously, information whether the patient received vasopressors medications, such as epinephrine, norepinephrine, phenylephrine, dopamine, or vasopressin, were collected. Skin pigmentation 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 ≤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 (≤300 and ≤150) and for patients with SpO2 ≤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.
References

[1] Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012; 307:2526–2533

[2] Fan Eddy., Brodie Daniel., Slutsky Arthur S. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA, 319(7), 698-710. doi:10.1001/jama.2017.21907

[3] Villar Jesús., Pérez-Méndez Lina., Blanco Jesús., Añón José Manuel., Blanch Lluís., Belda Javier., Santos-Bouza Antonio., Fernández Rosa Lidia., Kacmarek Robert M., Spanish Initiative for Epidemiology, Stratification, and Therapies for ARDS (SIESTA) Network. (2013). A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting--a prospective, multicenter validation study. Intensive Care Med, 39(4), 583-92. doi:10.1007/s00134-012-2803-x

[4] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007 Aug;132(2):410-7. Epub 2007 Jun 15. PubMed PMID:17573487.

[5] Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. Anesthesiology. 2005 Apr;102(4):715-9. PubMed PMID: 15791098.

[6] Brown SM, Duggal A, Hou PC, Tidswell M, Khan A, Exline M, Park PK, Schoenfeld DA, Liu M, Grissom CK, Moss M, Rice TW, Hough CL, Rivers E, Thompson BT, Brower RG; National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. Non-linear Imputation of PaO2/FIO2 From SpO2/FIO2 Among Mechanically Ventilated Patients in the ICU: A Prospective, Observational Study. Crit Care Med. 2017 Aug;45(8):1317-1324. doi: 10.1097/CCM.0000000000002514. PubMed PMID: 28538439; PubMed Central PMCID: PMC5511089.

[7] Brown, Samuel M. et al. “Non-linear Imputation of Pao2/Fio2 From Spo2/Fio2 Among Patients with Acute Respiratory Distress Syndrome.” Chest 150.2 (2016): 307–313. PMC. Web. 13 Aug. 2018.

[8] Feiner JR, Severinghaus JW, Bickler PE. Dark skin decreases the accuracy of pulse oximeters at low oxygen saturation: the effects of oximeter probe type and gender. Anesth Analg. 2007 Dec;105(6 Suppl: S18-23, tables of contents. PubMed PMID: 18048893.

[9] Pandharipande PP, Shintani AK, Hagerman HE, St Jacques PJ, Rice TW, Sanders NW, Ware LB, Bernard GR, Ely EW. Derivation and validation of Spo2/Fio2 ratio to
impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Crit Care Med. 2009 Apr;37(4):1317-21. doi: 10.1097/CCM.0b013e31819cefa9. PMID: 19242333; PMCID: PMC3776410.

[10] Ellis RK. Determination of PO2 from saturation. J Appl Physiol (1985). 1989 Aug;67(2):902. doi: 10.1152/jappl.1989.67.2.902. PMID: 2793692.

[11] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988 Sep;44(3):837-45. PMID: 3203132.

[12] R Core Team (2020). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
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

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

- Tablesfiguresandsupplement.pdf