Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4292-24
Intern Med Advance Publication
http://internmed.jp

【 ORIGINAL ARTICLE 】

Predictive Value of the PaO_2/FIO_2 Ratio for Mortality in Patients with Acute Respiratory Distress Syndrome: A Systematic Review and Meta-analysis

Satoshi Yoshimura[1,2], Katsuhiko Hashimoto[3], Yuji Shono[4], Takahiro Tamura[5], Ryo Uchimido[6], Koichi Ando[7], Satoshi Okamori[8], Takuo Yoshida[9], Shigenori Yoshitake[10] and Yohei Okada[1,11];
on behalf of the Japanese ARDS Clinical Practice Guideline Systematic Review Task Force

Abstract:

Background Despite the controversy regarding its clinical utility, the PaO_2/FIO_2 ratio has been used to define the severity of acute respiratory distress syndrome (ARDS). This systematic review and meta-analysis (SRMA) details summary estimates of the predictive performance of PaO_2/FIO_2 ratio in predicting mortality in patients with ARDS.

Methods To clarify the integrated diagnostic accuracy, we included studies in which the study population comprised patients with ARDS in any clinical setting, included adult patients (≥18 years old), and evaluated mortality. The MEDLINE and Cochrane Central Registry of Controlled Trials databases were searched for articles in English. We performed SRMA on the accuracy of the diagnostic prognostic tests using the Quality Assessment of Diagnostic Accuracy Studies-2 tool to evaluate the risk of bias. We obtained summary point estimates of sensitivity and specificity and calculated the area under the receiver operating characteristic (AUROC) curve of the summary receiver operating characteristic curve with 95% confidence intervals (CIs).

Results Twenty-eight trials with 38270 patients were included in the quality assessment. Most of the studies were conducted in intensive-care units. Overall, the risk of bias is high. For PaO_2FIO_2 of 100 and 200 the pooled sensitivity, specificity, and AUROC were 44.8% (95% CI, 38.1%-51.7%), 70.6% (95% CI, 65.9%-74.9%), 0.60 (0.58-0.64) and 83.9% (95% CI, 78.9%-87.8%), 26.1% (95% CI, 20.8%-32.1%), 0.64 (0.60-0.69), respectively.

Conclusion The PaO_2/FIO_2 ratio alone did not have impressive prediction accuracy for mortality in patients with ARDS and might not be able to be used solely as a clinical prognostic tool.

Key words: emergency medicine, critical care, intensive care, systematic review, meta-analysis, acute respiratory distress syndrome

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.4292-24)

[1]Department of Preventive Services, School of Public Health, Kyoto University, Japan, [2]Department of Emergency Medicine, Rakuwakai Otowa Hospital, Japan, [3]Department of Minimally Invasive Surgical and Medical Oncology, Fukushima Medical University, Japan, [4]Emergency and Critical Care Center, Kyushu University Hospital, Japan, [5]Department of Anesthesiology, Nagoya University Graduate School of Medicine, Japan, [6]Department of Intensive Care Medicine, Tokyo Medical and Dental University, Japan, [7]Division of Respiratory Medicine and Allergology, Department of Medicine, Showa University School of Medicine, Japan, [8]Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Japan, [9]Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Japan, [10]Department of Health Science, Kyushu University of Health and Welfare, Japan and [11]Department of Primary Care and Emergency Medicine, Graduate School of Medicine, Kyoto University, Japan

Received: June 25, 2024; Accepted: October 10, 2024; Advance Publication by J-STAGE: December 5, 2024
Correspondence to Dr. Yohei Okada, yokada-kyf@umin.ac.jp

Introduction

Acute respiratory distress syndrome (ARDS) is a condition of acute lung injury related to inflammation and is characterized by high pulmonary vascular permeability and a high amount of extrapulmonary water (1). To evaluate the severity of ARDS, the PaO_2/FIO_2 ratio is commonly used in the clinical setting according to the Berlin definition, reported in 2012 (2). Although the classification of severity is not the same as the prognostic power of mortality, the association between the severity of the Berlin definition and the prognosis has been evaluated in several studies (3-5). In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure study, the 28-day survival decreased with increasing severity of illness stratified according to the Berlin definition (3).

Recently, a retrospective study conducted in Japan also suggested an association between PaO_2/FIO_2 and the 30-day mortality (4). However, another study showed that the severity of respiratory failure was not associated with patient mortality (6). The original study of the Berlin definition reported that PaO_2/FIO_2 had a poor predictive value for mortality, with an area under the receiver operating characteristic (AUROC) curve of 0.577 (95% confidence interval [CI], 0.561-0.593) (2).

Although the clinical utility of PaO_2/FIO_2 remains controversial, to our knowledge, its predictive accuracy for mortality has not been systematically reviewed. Determining the integrated prognostic accuracy between the PaO_2/FIO_2 ratio and the prognosis in patients with ARDS may be useful for stratifying patients and allocating appropriate medical resources in emergency medicine and intensive-care settings.

The primary objective of this study was to obtain summary estimates of predictive performance, including sensitivity and specificity, and the AUROC curve of the summary receiver operating characteristic curve with 95% CIs among studies on PaO_2/FIO_2 for the prediction of any type of mortality in patients diagnosed with ARDS.

Materials and Methods

We performed a systematic review and meta-analysis (SRMA) of studies on the accuracy of prognostic tests. We adhered to the methodological standards outlined in the Handbook for Diagnostic Test Accuracy (DTA) Reviews of Cochrane (7) and used the Preferred Reporting Items for Diagnostic Test Accuracy Studies (PRISMA-DTA) (8) to report our findings. The review protocol was predefined, and a post hoc analysis was referred to in this study Although the protocol has not been published or registered, the study outline was prospectively registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN:000041058). The need for ethical approval and patient consent for the analysis and publication was waived owing to the nature of the SRMA. The whole method in this study was based on the preprint version of our study (See "*Ethics approval and consent to participate*" in Declarations).

Study eligibility criteria

The study population included patients with ARDS in any setting, including the emergency department, general hospital ward, and intensive-care unit (ICU). The index test was the PaO_2/FIO_2 ratio or the oxygenation index. We included studies on adult patients (aged ≥18 years) and evaluated their mortality rates. The reference standard for this study was the mortality rate reported for each study. We included all abstracts and full-text articles in English that described retrospective and prospective observational studies and randomized and quasi-randomized controlled trials. We excluded case reports, case series, animal studies, and pediatric studies. For studies that used the same database, we only included those with more patients.

Data source and search method

We searched two electronic databases (MEDLINE and Cochrane Central Register of Controlled Trials) for studies published before June 19, 2020. The search was performed using the following terms: "respiratory distress syndrome," "adult," and "acute lung injury." acute lung injury. The details of the search strategy are reported in the Supplementary Material. In the first phase, study data were collected using Rayyan QCRI (9). Titles was imported into Rayyan QCRI directly from MEDLINE and the Cochrane Central Register of Controlled Trials, and duplicates were removed. In the first phase, two paired reviewers (S. Yoshimura and Y.S.; S. Yoshitake and K.H.) independently screened the titles and abstracts of all identified studies. Disagreements were resolved by consensus, and no third-party adjudication was necessary. In the second phase, three paired reviewers (S. Yoshimura and Y. S.; S. Yoshitake and K.H.; Y.O. and T.T.) independently applied the eligibility criteria to the full text of the selected articles from the first phase and reported the reasons for exclusion. Disagreements were resolved by discussion with a third reviewer. We needed a 2×2 table of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) results extracted from the original article or calculated from other available information from each study in the meta-analysis. We contacted the authors for 2×2 table counts if we were unable to obtain relevant values from the reported data. Studies were excluded if the corresponding author did not respond after our contact attempts.

Data extraction and quality assessments

We used a predefined data collection form for the study characteristics and outcome data, which were tested in at least three studies in the review. Three pairs (S. Yoshimura and Y.S.; S. Yoshitake and K.H.; Y.O. and T.T.) extracted data on the study characteristics from the included studies. We extracted information regarding the following study characteristics: author information, year of publication, study

design, eligibility criteria, number of patients included, mean or median age, threshold used for patient stratification by PaO_2/FIO_2, and mortality.

The shortest outcome was selected if the study had reported several outcomes. We also extracted or calculated the predictive accuracy parameters, TP, FP, TN, and FN. Two investigators evaluated the risk of bias using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (10), which is widely accepted and includes four domains of risk of bias and three domains of applicability.

Data synthesis and statistical analyses

• **Primary analyses**

We represented the results of individual studies by plotting sensitivity and specificity estimates with 95% CIs on forest plots and visually assessing heterogeneity. To pool the results, we applied a bivariate model and obtained summary point estimates of sensitivity and specificity with 95% CIs. We also presented a summary of the receiver-operating characteristic (SROC) curve and evaluated the area under the SROC curve and Higgins I-squared as ad hoc analyses.

• **Sensitivity analyses**

Sensitivity analyses were performed as post hoc analyses to evaluate the robustness of the results. First, we performed a sensitivity analysis by the year of publication for studies published after the Berlin definition was established. Second, we performed the same analysis as the primary analysis between studies that used the Berlin definition as the inclusion criteria for patients with ARDS. We planned a subgroup analysis based on the etiology of ARDS but could not perform this analysis because each study included various etiologies, and we could not obtain individualized data on the etiology.

All analyses were performed using the Review Manager 5.3 software program (Cochrane Collaboration, London, UK), RStudio Version 1.4.1106, and the Meta-DTA Meta-Analysis application (11).

Results

Search results

In total, 4055 studies were included. Twenty-eight studies (2, 4, 5, 12-36) and 38270 patients met the eligibility criteria and were included in the quality assessment (Fig. 1).

Study characteristics

Of the included studies, 27 were cohort studies (non-randomized studies), and the remaining were randomized controlled trials. No case-control studies were included. The median sample size for all included studies was 401 patients (interquartile range: 193-988 patients). Most study settings were in the ICU. The patient characteristics, country, index test definitions, reference standards used in each study, and outcomes are summarized in Table 1. The PaO_2/FIO_2 ratio was evaluated on the day of the ARDS diagnosis in the 24 studies. The other evaluation of PaO_2/FIO_2 was performed 1 day after the day of the diagnosis (1 study), 24 h after the day of the ARDS diagnosis (2 studies), and 3 days after ARDS diagnosis (1 study). Regarding outcome measures, 16 studies analyzed in-hospital mortality, 6 studies evaluated the ICU mortality, 2 studies evaluated the 28-day mortality, 4 studies evaluated the 30-day mortality, 2 evaluated the 60-day mortality, 2 evaluated the mortality (undefined), 1 assessed the 90-day mortality, and 1 evaluated the 100-day mortality.

Quality assessments

The quality assessment using the QUADAS-2 criteria is shown in Fig. 2. One study (3.6%) had an unclear risk of bias in patient selection because it included only patients with a PaO_2/FIO_2 ratio <173. One study (3.6%) had a high risk of bias in patient selection because it excluded patients without data on mean airway pressure or PaO_2/FIO_2.

Five studies (17.9%) had an unclear risk of bias in the index test because it was unknown whether the reference standard was blinded when the assessors interpreted the index test or whether the cutoff of the index test was prespecified. Twenty-four studies (85.7%) had an unclear risk of bias in the reference standard, because it was unclear whether the reference standard was interpreted when the results of the index test were blinded. The details of the assessment of the risk of bias are shown in Fig. 2. The overall risk of bias in the included studies was high because 1 study had a high risk of bias and 24 had an unknown risk of bias.

Results of synthesis

• **Primary analyses**

The pooled sensitivity of PaO_2/FIO_2 across all included studies for a PaO_2/FIO_2 ratio of 100 was 44.8% (95% CI, 38.1%-51.7%), and the specificity was 70.6% (95% CI, 65.9%-74.9%). The pooled sensitivity of PaO_2/FIO_2 across all included studies for a PaO_2/FIO_2 of 200 was 83.9% (95% CI, 78.9-87.8%), and the specificity was 26.1% (95% CI, 20.8%-32.1%). Forest plots of the sensitivity and specificity of each cutoff PaO_2/FIO_2 are shown in Fig. 3 (PaO_2/FIO_2 = 100) and Fig. 4 (PaO_2/FIO_2 = 200). The SROC curves, bivariate summary points of specificity and sensitivity, and 95% confidence regions for the PaO_2/FIO_2 ratio are shown in Figs. 5 and 6. The AUROC with the 95% CI of a PaO_2/FIO_2 of 100 was 0.60 (0.58-0.64), whereas the AUROC with the 95% CI of a PaO_2/FIO_2 of 200 was 0.64 (0.60-0.69). The Higgins I-squared values were 14.0% for PaO_2/FIO_2 100 and 27.1% for PaO_2/FIO_2 200.

• **Sensitivity analyses**

Table 2 shows the results of sensitivity and subgroup analyses. We performed sensitivity analyses by publication year for studies published after the Berlin definition was established. In this analysis, the sensitivity for a PaO_2/FIO_2 of 100 was 45.0% (95% CI, 37.9%-52.3%), and the specificity was 70.7% (95% CI, 65.9%-75.1%). The AUROC with the 95% CI was 0.60 (95% CI, 0.57-0.63). The sensitivity for a

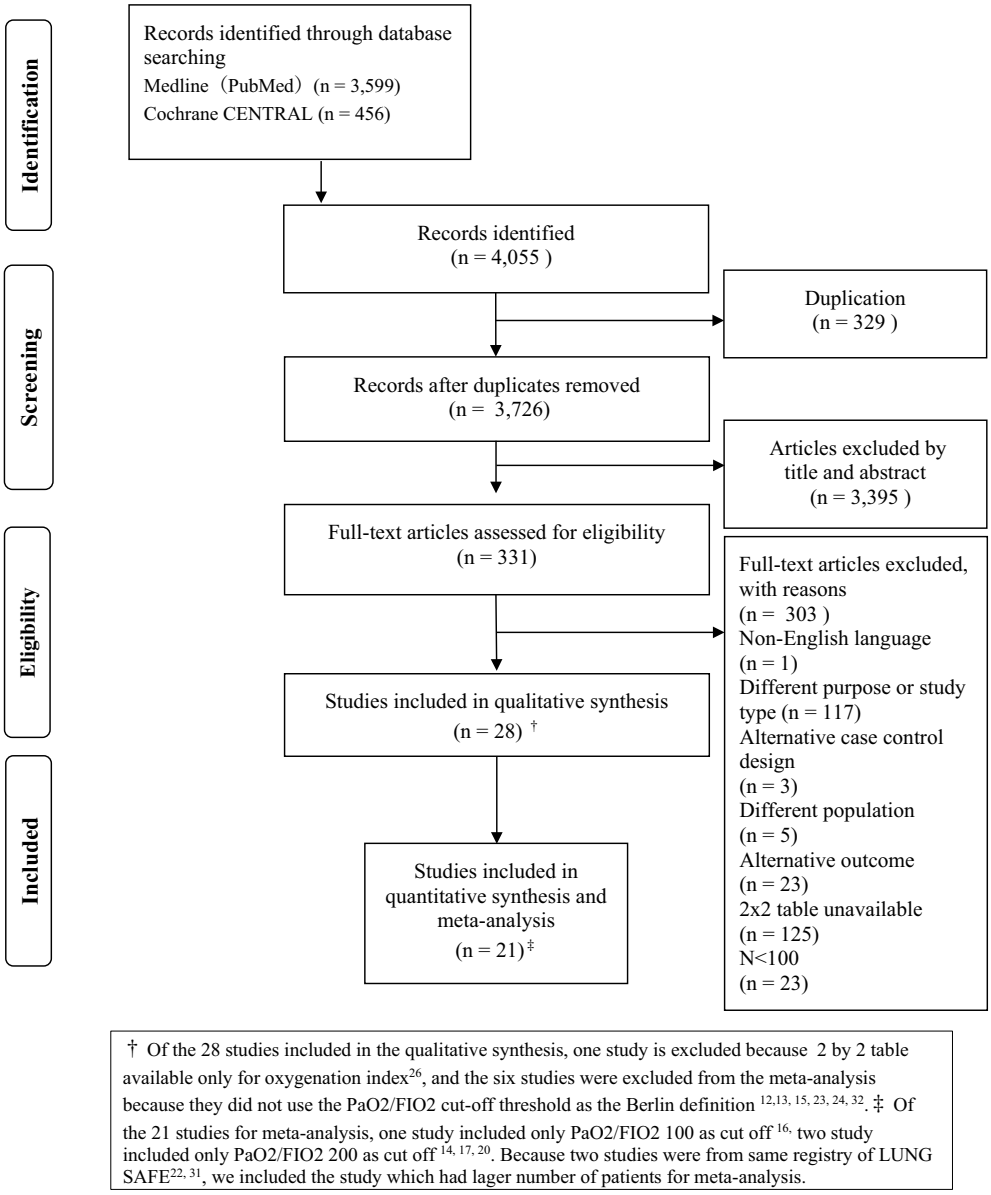

Figure 1. **Flow diagram of the literature selection process.**

Table. **Sensitivity and Subgroup Analysis.**

	Sensitivity	Specificity	AUROC
The studies published after Berline definition, % (95%CI)			
P/F ratio 100	45.0 (37.9-52.3)	70.7 (65.9-75.1)	0.60 (0.57-0.63)
P/F ratio 200	82.6 (77.0-87.1)	27.8 (22.6-35.0)	0.65 (0.60-0.70)
The studies which used Berlin definition as the inclusion criteria in each study			
P/F ratio 100	44.1 (36.8-51.7)	71.1 (66.0-75.7)	0.59 (0.57-0.62)
P/F ratio 200	82.3 (76.3-87.1)	28.5 (22.0-36.1)	0.64 (0.60-0.69)

AUROC: area under the receiveroperating characteristic, CI: confidence interval, P/F: PaO2/FiO2, ICU: intensive care unit

PaO_2/FIO_2 ratio of 200 was 82.6% (95% CI, 77.0%-87.1%), and the specificity was 27.8% (95% CI, 21.6%-35.0%). The AUROC with the 95% CI was 0.65 (95% CI, 0.60-0.70). We also conducted a subgroup analysis of the studies that used the Berlin definition as the inclusion criterion. Forest plots and SROC curves, together with bivariate summary points of specificity and sensitivity, and their 95% confidence regions for PaO_2/FIO_2 are shown in the supplementary material.

Figure 2. **The assessment of the risk of bias for individual studies.**

Discussion

Key observations

We conducted an SRMA to evaluate the prognostic value of the PaO_2/FIO_2 ratio in predicting mortality in adult patients with ARDS. The risk of bias was high among the included studies.

With a PaO_2/FIO_2 cutoff of 100, the sensitivity to predict mortality was 45.0%, and the specificity was 70.7%. With a PaO_2/FIO_2 cutoff of 200, the sensitivity to predict mortality was 82.6%, while the specificity was 27.8%. The results showed that PaO_2/FIO_2 alone with a cutoff of PaO_2/FIO_2 100 and 200 was not sufficient to predict mortality among ARDS patients with a low area under the SROC for PaO_2/FIO_2 ratios of 100 and 200 (an AUC 0.5 is no better than chance for a diagnostic test (37)).

Strength of the study compared to previous studies

This extensive literature review provides the best available assessment of the prognostic accuracy of PaO_2/FIO_2. An ex-

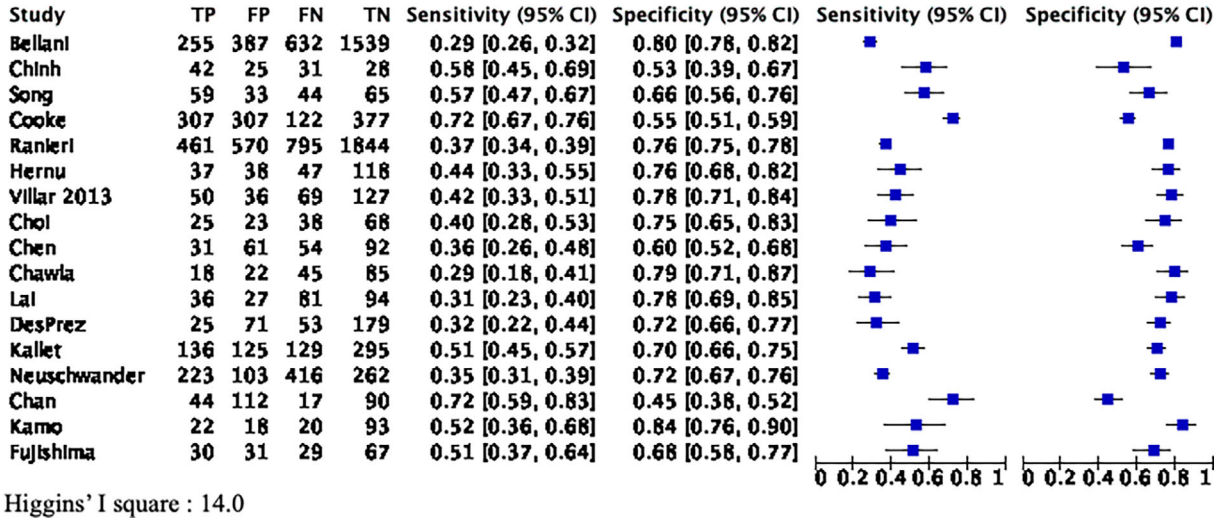

Figure 3. **Forest plots show the sensitivity and specificity of the PaO_2/FIO_2 (cutoff of 100) in the 18 included studies.**

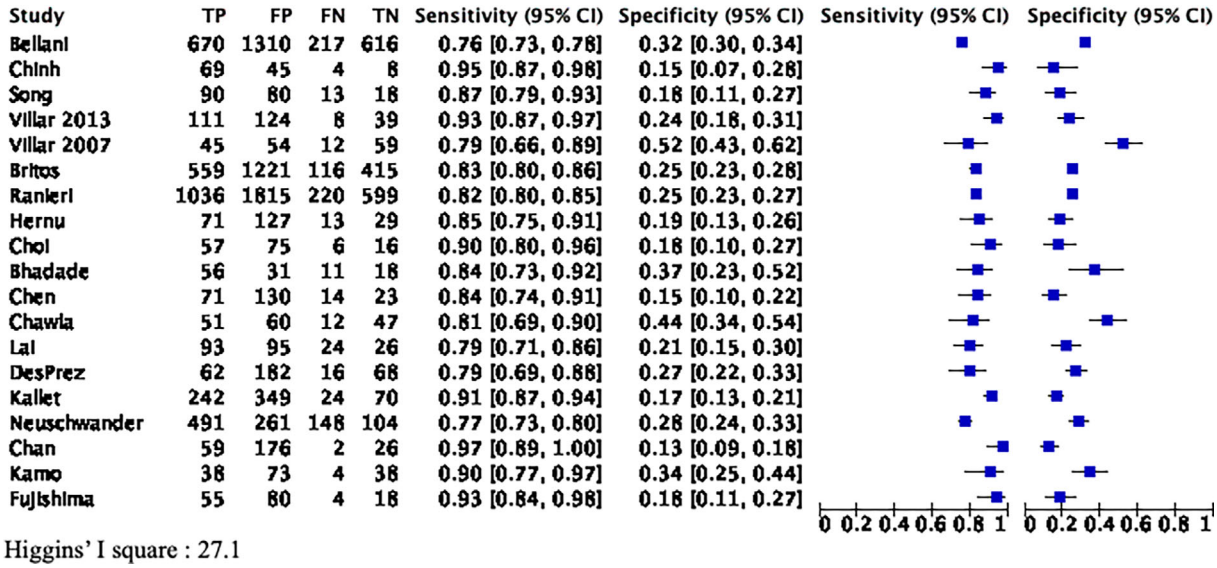

Figure 4. **Forest plots showing the sensitivity and specificity of the PaO_2/FIO_2 (cutoff of 200) in the 20 included studies.**

tensive search of PubMed and Cochrane databases did not reveal any existing systematic reviews or meta-analyses on the prognostic accuracy of PaO_2/FIO_2. To our knowledge, this is the first report on the prognostic value of the PaO_2/FIO_2 ratio in patients with ARDS.

Study implications

This extensive literature review provides the best available evidence for the prognostic accuracy of PaO_2/FIO_2. This study revealed that the prognostic accuracy of PaO_2/FIO_2 is not acceptable in clinical settings. Although the classification of severity is not the same as the prognostic power of mortality, several studies have investigated the prognostic accuracy or association between PaO_2/FiO_2 ratio and prognostic outcomes. For example, a previous study showed that neither stratification by severity nor PaO_2/FiO_2 at study entry was independently associated with mortality (5). However, another study showed that the Berlin definition of severity classification with a PaO_2/FiO_2 of 100 is useful to identify patients with severe ARDS at high risk of death but may be less useful to differentiate between mild (PaO_2/FiO_2, 200-300) and moderate disease (PaO_2/FiO_2, 100-200) (4). The present study provides summarized and integrated results, including these studies (4, 5), and concluded that the PaO_2/FIO_2 might not be useful solely as a prognostic factor in the clinical setting.

Future direction of study area

The varying background characteristics and heterogeneity of patients with ARDS in this study may have influenced the results; therefore, it will be necessary to evaluate the heterogeneity of these backgrounds in future studies. In the

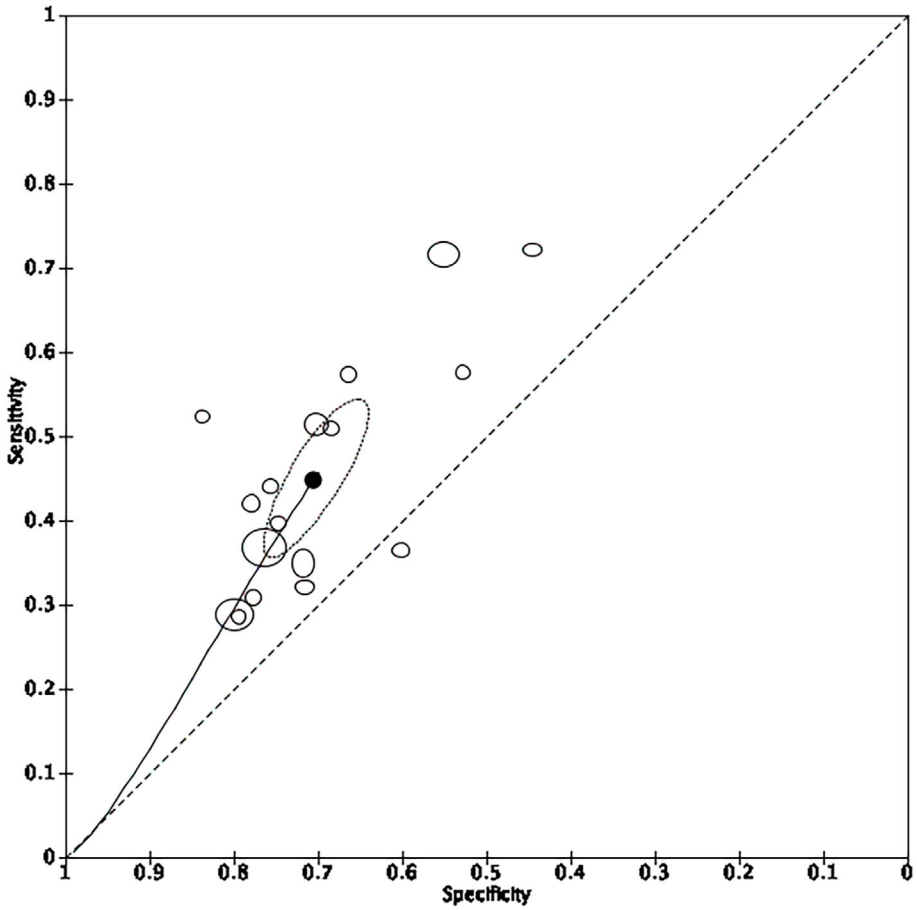

Figure 5. **Summary of the receiver-operating characteristic (SROC) curve with summary point estimates of sensitivity and specificity along with 95% confidence intervals (CIs) for a PaO_2/FIO_2 of 100. Black plot (with dotted circle): Represents the pooled estimate of sensitivity and specificity with its 95% CI. White plots: Show the individual sensitivity and specificity values reported from each study. Solid line: Depicts the SROC curve, summarizing the diagnostic accuracy across the included studies. Plot size: The size of each plot reflects the sample size of the respective study, meaning that larger circles correspond to studies with more participants, indicating their relative weight in the analysis.**

present study, a PaO_2/FIO_2 of 100 as the cutoff for death was neither sensitive nor highly specific, findings that were the same as in the subgroup analysis that focused on studies that used the Berlin definition for the inclusion of each study. This may be because the background diseases in ARDS in this study varied, and their heterogeneity may have affected the results. For example, in a study of ARDS after influenza infection (33), the sensitivity and specificity were 72% and 45%, respectively, for a PaO_2/FIO_2 ratio of 100, values that were lower than those of other studies, and it is possible that the variation of the primary disease in each study affected the results. As another example, the median (interquartile range) SOFA score in the entire patient population in the study by Fujishima et al (35). was 9.0 (7.0-13.0), while that in the study by Song et al (36). was 4.98 (4.65-5.30). The severity of ARDS in the patients included in the individual studies differed, suggesting that differences in background disease and severity of the disease may have affected the results because it influences the spectrum bias. Finally, the current review did not include the literature on ARDS with coronavirus disease 2019 (COVID-19), so more research concerning the performance of PaO_2/FIO_2 in patients with COVID-19 is required.

Limitations

Several limitations associated with the present study warrant mention. First, we did not assess the heterogeneity of the prognostic accuracy of the PaO_2/FIO_2 ratio within the study according to the primary causes of ARDS. The primary cause of ARDS varied among studies included in this meta-analysis. Furthermore, some studies have not described the primary causes. Second, several interventions included in the study may have affected mortality; however, this study did not focus on the investigation of causality but rather on the prediction or diagnostic accuracy of PaO_2/FIO_2. Third, we searched only for MEDLINE and the Cochrane Central Register of Controlled Trials and did not search for gray literature and did not search or non-English literature because

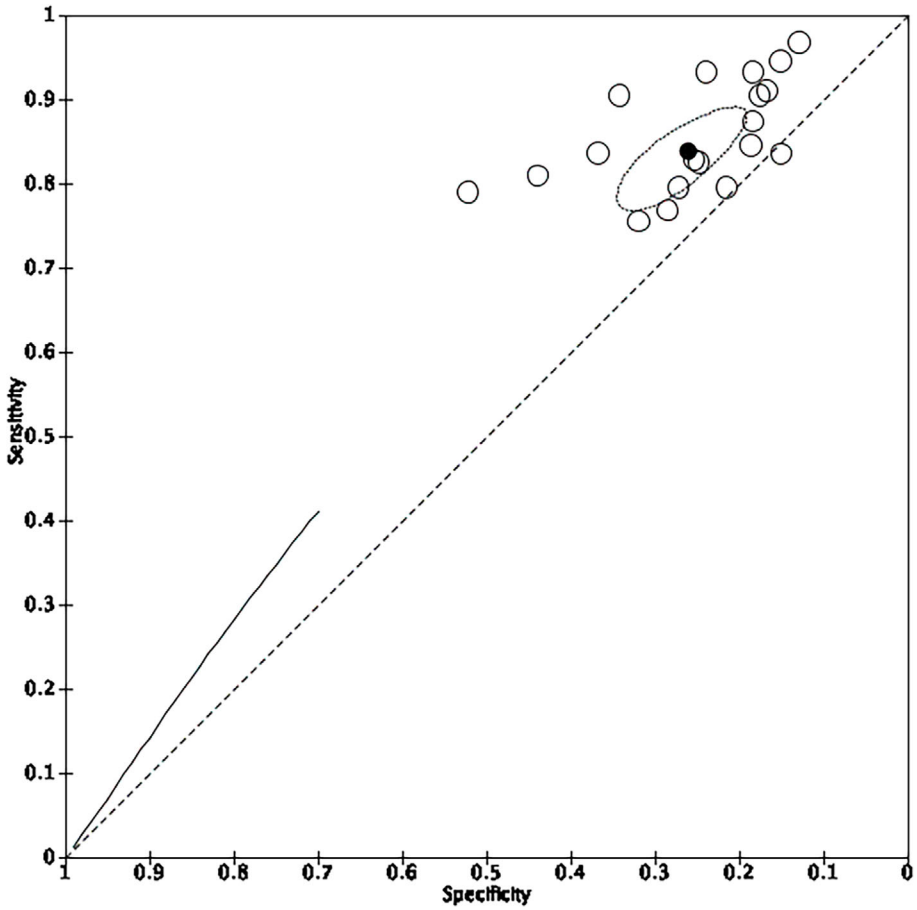

Figure 6. Summary of the receiver-operating characteristic (SROC) curve with summary point estimates of sensitivity and specificity with 95% confidence intervals (CIs) for a PaO_2/FIO_2 of 200. Black plot (with dotted circle): Represents the pooled estimate of sensitivity and specificity with its 95% CI. White plots: Show the individual sensitivity and specificity values reported from each study. Solid line: Depicts the SROC curve, summarizing the diagnostic accuracy across the included studies. Plot size: The size of each plot reflects the sample size of the respective study, meaning that larger circles correspond to studies with more participants, indicating their relative weight in the analysis.

of our limited recourse to databases; therefore, there may have been an omission in the selected literature. Fourth, this study focused on the PaO2/FIO2 ratio as the sole prognostic indicator. Although the PaO_2/FIO_2 ratio is a convenient and rapid measure with consistency and objectivity across different settings, it does not account for other prognostic factors that might provide a more comprehensive predictive model. The inclusion of additional factors such as patient-specific characteristics or other clinical indicators might be able to enhance the predictive power of future analyses. This will be the subject of further investigation in subsequent studies. Finally, the current study was conducted simultaneously with the analysis in clinical question (CQ) 3 of the ARDS Clinical Practice Guideline 2021 (38) and reflects the discussions involved in guideline development, yet it differs in several key aspects. First, the previous study included the same cohorts as the two studies (22, 31), but these cohorts were identical. In the present study, to avoid population overlap, only the newest and largest cohorts (31) were included. Second, a study (39) previously included in the guideline (38) was excluded from this analysis because the correct cutoff point was P/F 150, not P/F 100, as it was rounded to in the previous study. Consequently, the total number of studies included in the analysis decreased from 23 to 21. In addition, an analysis of an SROC curve was added to this study to make the results more visually understandable.

Conclusions

In conclusion, our SRMA found that PaO_2/FIO_2 does not have impressive prognostic accuracy for mortality. Based on our findings, PaO_2/FIO_2 may not be able to solely be used as a prognostic tool for mortality in clinical settings.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank all members of the Japanese ARDS Clinical Practice Guideline Committee of the Japanese Society of Respiratory Care Medicine, the Japanese Respiratory Society, and the Japanese Society of Intensive Care Medicine. We also thank the librarian at the Kyoto Prefectural University of Medicine Medical

Library for developing the search strategy.

Trial registration

The study was registered in UMIN (registration number UMIN 000041058).

Sources of funding and Disclosures

Funding for obtaining the print of medical literature was provided by the Japanese ARDS Clinical Practice Guideline Committee. No other funding was provided. The authors declare that they have no competing interests.

IRB information

The need for ethical approval and patient consent for analysis and publication was waived owing to the nature of the study design.

Ethics approval and consent to participate

The method used in this study was based on the preprint version (DOI: https://doi.org/10.21203/rs.3.rs-1042756/v2).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Funding

The Japanese ARDS Clinical Practice Guidelines Committee provided funding for obtaining medical literature. No other funding was received for the study.

Authors' contributions

Study design: all authors

Literature search: S. Yoshimura, K. H., Y.S., T. T., K. A., T. Y., S. Yoshitake and Y. O.

Screening: S. Yoshimura, K.H., Y.S., T.T., S. Yoshitake, and Y. O.

Data extraction: S. Yoshimura, K.H., Y.S., T.T., S. Yoshitake, and Y.O.

Quality assessment: S. Yoshimura, K. H., Y.S., T. T., S. O., S. Yoshitake and Y. O.

Analysis: S. Yoshimura and S.O.

Writing the draft: S. Yoshimura and Y.O.

All authors discussed the important intellectual content in the draft and revised the manuscript accordingly. All authors approved the final draft and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

References

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med **377**: 562-572, 2017.
2. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA **307**: 2526-2533, 2012.
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA **315**: 788-800, 2016.
4. Kamo T, Tasaka S, Suzuki T, et al. Prognostic values of the Berlin definition criteria, blood lactate level, and fibroproliferative changes on high-resolution computed tomography in ARDS patients. BMC Pulm Med **19**: 37, 2019.
5. Hernu R, Wallet F, Thiollière F, et al. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. Intensive Care Med **39**: 2161-2170, 2013.
6. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med **38**: 1573-1582, 2012.
7. Handbook for DTA reviews [Internet]. [cited 2021 May 10]. Available from: https://methods.cochrane.org/sdt/handbook-dta-reviews
8. PRISMA [Internet]. [cited 2021 May 10]. Available from: http://www.prisma-statement.org/Extensions/DTA
9. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev **5**: 210, 2016.
10. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med **155**: 529-536, 2011.
11. Freeman SC, Kerby CR, Patel A, et al. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test accuracy studies: MetaDTA. BMC Med Res Methodol **19**: 81, 2019.
12. Knaus WA, Sun X, Hakim RB, et al. Evaluation of definitions for adult respiratory distress syndrome. Am J Respir Crit Care Med **150**: 311-317, 1994.
13. Suchyta MR, Orme JFJ, Morris AH. The changing face of organ failure in ARDS. Chest **124**: 1871-1879, 2003.
14. Villar J, Pérez-Méndez L, López J, et al. An early PEEP/FIO_2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med **176**: 795-804, 2007.
15. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA **299**: 637-645, 2008.
16. Cooke CR, Kahn JM, Caldwell E, et al. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. Crit Care Med **36**: 1412-1420, 2008.
17. Britos M, Smoot E, Liu KD, et al. The value of positive end-expiratory pressure and Fio_2 criteria in the definition of the acute respiratory distress syndrome. Crit Care Med **39**: 2025-2030, 2011.
18. Villar J, Pérez-Méndez L, Blanco J, et al. A universal definition of ARDS: the PaO_2/FiO_2 ratio under a standard ventilatory setting--a prospective, multicenter validation study. Intensive Care Med **39**: 583-592, 2013.
19. Choi WI, Shehu E, Lim SY, et al. Markers of poor outcome in patients with acute hypoxemic respiratory failure. J Crit Care **29**: 797-802, 2014.
20. Bhadade R, de'Souza R, Harde M, et al. Mortality predictors of ARDS in medical Intensive Care Unit of a tertiary Care Centre in a tropical country. J Assoc Physicians India **63**: 16-22, 2015.
21. Chen W, Janz DR, Shaver CM, et al. Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/FIO_2 ratio compared with PaO_2/FIO_2 ratio. Chest **148**: 1477-1483, 2015.
22. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med **42**: 1865-1876, 2016.
23. Bos LD, Schouten LR, Cremer OL, et al. External validation of the APPS, a new and simple outcome prediction score in patients with the acute respiratory distress syndrome. Ann Intensive Care

6: 89, 2016.

24. Villar J, Ambrós A, Soler JA, et al. Age, PaO_2/FIO_2, and plateau pressure score: A proposal for a simple outcome score in patients with the acute respiratory distress syndrome. Crit Care Med **44**: 1361-1369, 2016.

25. Chawla R, Mansuriya J, Modi N, et al. Acute respiratory distress syndrome: predictors of noninvasive ventilation failure and intensive care unit mortality in clinical practice. J Crit Care **31**: 26-30, 2016.

26. Balzer F, Menk M, Ziegler J, et al. Predictors of survival in critically ill patients with acute respiratory distress syndrome (ARDS): an observational study. BMC Anesthesiol **16**: 108, 2016.

27. Lai CC, Sung MI, Liu HH, et al. The ratio of partial pressure arterial oxygen and fraction of inspired oxygen 1 day after acute respiratory distress syndrome onset can predict the outcomes of involving patients. Medicine **95**: e3333, 2016.

28. Neuschwander A, Lemiale V, Darmon M, et al. Noninvasive ventilation during acute respiratory distress syndrome in patients with cancer: trends in use and outcome. J Crit Care **38**: 295-299, 2017.

29. Kallet RH, Zhuo H, Ho K, et al. Lung injury etiology and other factors influencing the relationship between dead-space fraction and mortality in ARDS. Respir Care **62**: 1241-1248, 2017.

30. DesPrez K, McNeil JB, Wang C, et al. Oxygenation saturation index predicts clinical outcomes in ARDS. Chest **152**: 1151-1158, 2017.

31. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am J Respir Crit Care Med **195**: 67-77, 2017.

32. Shen Y, Cai G, Gong S, et al. Interaction between low tidal volume ventilation strategy and severity of acute respiratory distress syndrome: a retrospective cohort study. Crit Care **23**: 254, 2019.

33. Chan MC, Chao WC, Liang SJ, et al. First tidal volume greater than 8 mL/kg is associated with increased mortality in complicated influenza infection with acute respiratory distress syndrome. J Formos Med Assoc **118**: 378-385, 2019.

34. Chinh LQ, Manabe T, Son DN, et al. Clinical epidemiology and mortality on patients with acute respiratory distress syndrome (ARDS) in Vietnam. PLOS ONE **14**: e0221114, 2019.

35. Fujishima S, Gando S, Saitoh D, et al. Demographics, treatments, and outcomes of acute respiratory distress syndrome: the focused outcomes research in emergency care in acute respiratory distress syndrome, sepsis, and trauma (FORECAST) study. Shock **53**: 544-549, 2020.

36. Song M, Liu Y, Lu Z, et al. Prognostic factors for ARDS: clinical, physiological and atypical immunodeficiency. BMC Pulm Med **20**: 102, 2020.

37. Kottas M, Kuss O, Zapf A. A modified Wald interval for the area under the ROC curve (AUC) in diagnostic case-control studies. BMC Med Res Methodol **14**: 26, 2014.

38. Tasaka S, Ohshimo S, Takeuchi M, Yasuda H, Ichikado K, Tsushima K, et al. ARDS Clinical Practice Guideline 2021. J Intensive Care **10**: 32, 2022.

39. Shen Y, Cai G, Gong S, Dong L, Yan J, Cai W. Interaction between low tidal volume ventilation strategy and severity of acute respiratory distress syndrome: a retrospective cohort study. Crit Care **23**: 254, 2019.