Predictive Value of the PaO₂/FI_O₂ Ratio for Mortality in Patients with Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis

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Title: Predictive value of the PaO₂/FIO₂ ratio for mortality in patients with acute respiratory distress syndrome: A systematic review and meta-analysis

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Abstract

Background

PaO₂/FIO₂ (P/F) ratio has been used to define the severity of acute respiratory distress syndrome (ARDS) despite the controversy of its clinical utility. This systematic review and meta-analysis (SRMA) aimed to obtain summary estimates of predictive performance of the P/F ratio for predicting mortality in ARDS patients.

Methods

We included a study wherein the study population comprised ARDS patients in any clinical setting. Medline and Cochrane Central Registry of Controlled Trials were searched for all English language articles. We performed a SRMA on the accuracy of diagnostic prognostic tests using QUADAS-2 tool to evaluate the risk of bias. To pool the results, we applied the bivariate model and obtained summary point estimates of sensitivity and specificity with 95% CIs.

Results

Twenty-eight trials and 38270 patients were included in the meta-analysis. Most of the

study settings were in the intensive care units. The overall risk of bias was high. The pooled sensitivity of the P/F ratio in all included studies for a P/F ratio of 100 was 43.6% (95% CI, 36.9-50.5%) and the specificity was 71.1% (95% CI, 66.7-75.1%) and those for a P/F ratio of 200 were 83.2% (95% CI, 78.2-87.2%) and 26.2% (95% CI, 21.2-31.9%).

Interpretation

The P/F ratio had high sensitivity and moderate specificity at a P/F ratio of 200 and 100 respectively., which supports the use of the P/F ratio for screening ARDS patients who are at risk of deterioration.

Trial registration: The study was registered in UMIN with registration number 000041058.

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 ARDS severity, the $\text{PaO}_2/\text{FIO}_2$ (P/F) ratio is commonly used in the clinical setting according to the Berlin definition, reported in 2012, and the P/F ratio is used to define ARDS severity [2]. Subsequently, the association between the severity of Berlin definition and 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 by the Berlin definition [3]. Recently, a retrospective study conducted in Japan also suggested an association between P/F ratio and 30-day mortality [4].

However, another previous study showed that the severity of respiratory failure was not associated with patient mortality [6]. The original study of the Berlin Definition reported that the P/F ratio had a poor predictive value for mortality, with an area under the receiver operating curve of 0.577 (95% confidence interval [CI], 0.561-0.593) [2].

Although the clinical utility of the P/F ratio remains controversial in literature, its predictive accuracy for mortality has not been systematically reviewed to the best of our knowledge. Determining the integrated prognostic accuracy between the P/F ratio and prognosis in ARDS patients may be useful in stratifying patients and allocating appropriate medical resources in emergency medicine and intensive care settings. The primary objective of the current study was to obtain summary estimates of predictive performance, including sensitivity and specificity, across studies of P/F ratio for the prediction of any type of mortality in patients diagnosed with ARDS.

Methods

We performed a systematic review and meta-analysis (SRMA) of studies on the accuracy of the 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 of Diagnostic Test Accuracy Studies (PRISMA-DTA) [8] for reporting our findings. The review protocol was prospectively registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN: 000041058). The need for ethical approval and patient consent for analysis and publication was waived because of the nature of the SRMA

109

110 *Study eligibility criteria*

111 We included a study wherein the study population comprised ARDS patients in any
112 setting, including emergency departments, general hospital wards, and intensive care
113 units (ICUs). The index test was the P/F ratio or oxygenation index. We included studies
114 that involved adult patients (aged ≥ 18 years) and evaluated mortality. The reference
115 standard for this study was the mortality rates reported in each study. We included all
116 English-language abstracts and full-text articles describing retrospective and prospective
117 observational studies as well as randomized and quasi-randomized controlled trials. We
118 excluded case reports, case series, animal studies, and pediatric studies. We included
119 only the study with more patients for studies that used the same database.

120

121 *Data source and search method*

122 We searched two electronic databases (MEDLINE and the Cochrane Central Register of
123 Controlled Trials) for studies published before June 19, 2020. The search was conducted
124 using the terms “respiratory distress syndrome,” “adult,” and “acute lung injury.” The
125 details of the search strategy are reported in Supplement 1. In the first phase, study data
126 were collected using Rayyan QCRI [9]. Titles were 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 the identified studies. Disagreements were resolved by consensus, and no third-party adjudication was necessary. In the second phase, two 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 through discussion with a third reviewer. We needed to have a 2×2 table of true-positive, false-positive, true-negative, and false-negative results, either extracted from the original article or calculated from other available information from each study in the meta-analysis. We contacted authors for 2×2 table counts if we could not obtain the relevant values from the reported data. If the corresponding author did not respond after our attempts at contact, the study was excluded.

Data extraction and quality assessment

We used a pre-defined data collection form for study characteristics and outcome data, which were piloted on at least three studies in the review. Two review authors (S.

Yoshimura and Y.S., S. Yoshitake and K.H., Y.O., and T.T.) extracted data on study characteristics from the included studies. We extracted information on 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 the P/F ratio, and mortality.

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

Data Synthesis and Statistical Analysis

Primary analysis

We depicted the results of individual studies by plotting sensitivity and specificity estimates with 95% CIs on forest plots (ordered by the sensitivity of a P/F ratio of 200 and specificity of a P/F ratio of 100) and visually assessing the heterogeneity. To pool the results, we applied the 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.

Sensitivity analysis

Sensitivity analysis was performed as a post-hoc analysis to evaluate the robustness of the results. First, we performed the same analysis as the primary analysis among the studies that used the Berlin definition as the inclusion criteria for ARDS patients. Second, we performed the analysis among the studies that reported mortality as a short-term outcome (in-hospital, ICU, 28-day, and 30-day) because the short-term outcome was the relevant outcome, and mortality as the long-term outcome would be affected by factors that were not involved in the acute medical setting.

Results

Search results

A total of 4055 studies were screened. Twenty-eight studies [2, 4, 5, 11-34] and 38270 patients met the eligibility criteria and were included in the quality assessment (Figure 1).

Study characteristics

Of the included studies, 27 were cohort studies, and the remaining one study was a

randomized controlled trial. No case-control studies were included. The median sample size for all included studies was 401 patients (interquartile range, 193–988 patients). Most of the study settings were in the ICU. Patient characteristics, country, index test definitions, reference standards used in each study, and outcomes are summarized in Table 1. The P/F ratio was evaluated on the day of ARDS diagnosis in 24 studies. The other time of evaluating the P/F ratio was one day after the day of diagnosis (one study), 24 h after the day of ARDS diagnosis (two studies), and 3 days after ARDS diagnosis (one study). For outcome measures, 16 studies analyzed in-hospital mortality, 6 studies evaluated ICU mortality, 2 studies evaluated 28-day mortality, 4 studies evaluated 30-day mortality, 2 studies evaluated 60-day mortality, 2 studies evaluated mortality, which was not defined, one study assessed 90-day mortality, and one study evaluated 100-day mortality.

Quality assessment

Quality assessments using the QUADAS-2 criteria are shown in Figure 2. One study (3.6%) had an unclear risk of bias in patient selection because the study included only patients with a P/F ratio of <173 . One study (3.6%) had a high risk of bias in patient selection because the study excluded patients without data of mean airway pressure or

P/F ratio.

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 cut-off of the index test was prespecified or not. 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 in a situation where the results of the index test were blinded. Details of the assessment of the risk of bias are shown in Figure 2. The overall risk of bias in the included studies was high because there was only one study with high risk of bias and 24 studies with unknown risk of bias.

Results of Synthesis

Primary analysis

The pooled sensitivity of the P/F ratio across all included studies for a P/F ratio of 100 was 43.6% (95% CI, 36.9-50.5%) and the specificity was 71.1% (95% CI, 66.7-75.1%). The pooled sensitivity of the P/F ratio across all included studies for a P/F ratio of 200 was 83.2% (95% CI, 78.2-87.2%), and the specificity was 26.2% (95% CI, 21.2-31.9%). Forest plots of the sensitivity and specificity of each cut-off P/F ratio are shown in Figure 3 (a P/F ratio of 100) and Figure 4 (a P/F ratio of 200). The SROC curves,

together with bivariate summary points of specificity and sensitivity, and their 95%

confidence regions for the P/F ratio are shown in Figures 5 and 6.

Sensitivity analysis

We conducted a sensitivity analysis by publication year for the studies published after the

Berlin definition was established. In this analysis, the sensitivity for a P/F ratio of 100

was 43.1% (95% CI, 36.0-50.5%) and the specificity was 71.7% (95% CI, 66.8-76.1%).

The sensitivity for a P/F ratio of 200 was 82.0% (95% CI, 76.5-86.4%) and the specificity

was 27.9% (95% CI, 22.1-34.5%). We also conducted subgroup analysis for mortality as

the short-term outcome: ICU, in-hospital, 28-day, and 30-day mortality. In this analysis,

the sensitivity for a P/F ratio of 100 was 40.4% (95% CI: 33.1-48.2%) and the specificity

was 72.6% (95% CI: 67.1-77.5%). The sensitivity for a P/F ratio of 200 was 82.0% (95%

CI: 75.9-86.8%) and the specificity was 28.9% (95% CI: 23.0-35.7%). In addition, the

sensitivity analysis was performed for mortality as the short-term outcome: ICU, in-

hospital, 28-day, and 30-day mortality. Among studies that used the Berlin definition as

the inclusion criteria, the sensitivity for a P/F ratio of 100 was 41.5% (95% CI 34.0-

49.3%) and the specificity was 73.2% (95% CI: 67.3-78.4%). The sensitivity for an P/F

ratio of 200 was 81.7% (95% CI: 75.2-86.9%) and the specificity was 29.7% (95% CI:

23.5-36.8%). The forest plots and SROC curves, together with bivariate summary points

of specificity and sensitivity and their 95% confidence regions for the P/F ratio, are shown in the supplementary data.

Interpretation

Key observation

We conducted a SRMA to evaluate the prognostic value of the P/F ratio for predicting mortality in adult patients with ARDS. The risk of bias in the included studies was high. With a P/F ratio of 100 as the cutoff, the sensitivity for predicting mortality was low and the specificity was moderate. Of note, with a P/F ratio of 200 as the cutoff, the sensitivity for predicting mortality was high, while the specificity was low.

Strength of the study in comparison with previous studies

This extensive review of the literature provides the best available assessment of the prognostic accuracy of the P/F ratio. An extensive search conducted in the PubMed and Cochrane databases did not reveal any existing systematic reviews and meta-analyses on the prognostic accuracy of the P/F ratio. To the best of our knowledge, this is the first SRMA of the prognostic value of the P/F ratio in ARDS patients. Another strength of our study is that we were able to collect and analyze a comprehensive set of studies in which

the P/F ratio and outcome could be evaluated, and we were able to show the integrated sensitivity and specificity of the P/F ratio rather than the single diagnostic performance of the P/F ratio in individual studies. As for the stratification of ARDS patients by the P/F ratio, which is also used in the Berlin definition, the sensitivity of a P/F ratio of 200 is relatively high, which may be useful for screening ARDS patients at high risk of death. The number of ICU beds, ventilators, and medical staff is limited, and appropriate allocation of medical resources may become possible based on the P/F ratio. In addition, the specificity of a P/F ratio of 100 was low, and prognosis should not be considered based on the P/F ratio alone.

Future direction area of study

The varying background characteristics and heterogeneity of ARDS patients in this study may have influenced the results; therefore to evaluate heterogeneity of these backgrounds for the results will be mandated in the future study. In the present study, a P/F ratio of 100 as the cutoff for death was neither sensitive nor highly specific, which was the same as that in the subgroup analysis that focused on mortality as the short-term outcome and in the subgroup analysis of the study that used the Berlin definition. This may be due to the fact that 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

[31], the sensitivity and specificity were 72% and 45%, which 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 conducted by Fujishima et al. [33] was 9.0 [7.0-13.0], whereas that in the study conducted by Song et al. [34] 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 illness may have affected the results because it influences spectrum bias. Lastly, the current review did not include literature on ARDS with coronavirus disease (COVID)-19, and further research is mandated on the performance of the P/F ratio in patients with COVID-19.

Limitations

First, we did not assess the heterogeneity of the prognostic accuracy of the P/F ratio within the study by primary causes of ARDS. The primary cause of ARDS varied in the studies included in this meta-analysis. Furthermore, some studies have not described the primary causes. Second, we searched only MEDLINE and the Cochrane Central Register of Controlled Trials and did not search for gray literature; therefore, there may have been omission in the selected literature.

290

291 **Conclusions**

292 In conclusion, our SRMA found that the P/F ratio had poor sensitivity and moderate
293 specificity at a P/F ratio of 100, whereas at a P/F ratio of 200, it was sensitive but poorly
294 specific for mortality. Our findings support the continued use of a P/F ratio of 200 for
295 screening patients with ARDS who are at risk of deterioration.

296

297 **List of abbreviations**

298 ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID, coronavirus
299 disease; DTA, diagnostic test accuracy; FP, false positive; FN, false negative; ICUs,
300 intensive care units; P/F, PaO₂/FIO₂; PRISMA, Preferred Reporting Items for a
301 Systematic Review and Meta-analysis; QUADAS-2: Quality Assessment tool for
302 Diagnostic Accuracy Studies-2; SROC: summary of receiver-operating characteristic;
303 TP: true positive; TN: true negative.

304

305 **Declarations**

306 *Ethics approval and consent to participate*

307 Not applicable

308

309 *Consent for publication*

310 Not applicable

311

312 *Availability of data and materials*

313 The data used for this meta-analysis were obtained from articles corresponding to the
314 references in our list of references.

315

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317 The authors declare that they have no competing interests.

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323 *Authors' contributions*

324 Study design: All authors

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

326 Screening: S. Yoshimura, K.H., Y.S., T.T., S. Yoshitake, and Y.O.
327 Data extraction: S. Yoshimura, K.H., Y.S., T.T., S. Yoshitake, and Y.O.
328 Quality assessment: S. Yoshimura, K.H., Y.S., T.T., S.O., S. Yoshitake and Y.O.
329 Analysis: S. Yoshimura and S.O.
330 Writing the draft: S. Yoshimura and Y.O.
331 All authors discussed the important intellectual content in the draft and revised the
332 manuscript. All authors approved the final draft and agreed to be accountable for all
333 aspects of the work in ensuring that questions related to the accuracy or integrity of any
334 part of the work are appropriately investigated and resolved.

335

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342

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Figure Legends

Figure 1

Flow diagram of the literature selection process.

Figure 2

Risk of bias assessment for individual studies.

Figure 3

Forest plots showing the sensitivity and specificity of the P/F ratio (cutoff 100) in the 18 included studies.

Figure 4

Forest plots showing the sensitivity and specificity of the P/F ratio (cutoff 100) in the 20 included studies.

Figure 5

Summary of the receiver-operating characteristic (SROC) curve with summary point estimates of sensitivity and specificity with 95% confidence intervals (CIs) for a P/F ratio of 100.

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 P/F ratio of 200.

Additional files information

File name: Spplement1_protocol

File format: .pdf, .docx.

Title of data: Predictive value of the PaO₂/FIO₂ ratio for mortality in patients with acute respiratory distress syndrome: A systematic review and meta-analysis: Protocol

Description of data: Study protocol

File name: Spplement2

File format: .pdf, .docx.

485 Title of data: Sensitivity analysis: Forest plots and SROC curves, together with bivariate
486 summary points of specificity and sensitivity and their 95% confidence intervals.
487 Description of data: results of sensitivity analysis
488

Figures

Figure 1

Flow diagram of the literature selection process.

	Risk of bias domains				
	D1	D2	D3	D4	Overall
Study					
Knaus 1994	+	-	-	+	-
Suchyta 2003	-	+	-	+	-
Villar 2007	+	+	-	+	-
Meade 2008	+	-	-	+	-
Cooke 2008	+	-	-	+	-
Britos 2011	+	-	+	+	-
Ranieri 2012	+	+	+	+	+
Hernu 2013	+	+	-	+	-
Villar 2013	+	+	-	+	-
Choi 2014	+	+	-	+	-
Bhadade 2015	+	+	-	+	-
Chen 2015	+	+	-	+	-
Laffey 2016	+	+	-	+	-
Go 2016	+	+	-	+	-
Villar 2016	+	+	-	+	-
Lazzeri 2016	+	+	-	+	-
Balzer 2016	+	+	-	+	-
Lai 2016	+	+	-	+	-
Neuschwander 2017	+	+	-	+	-
Kallet 2017	+	+	-	+	-
DesPrez 2017	✗	+	-	+	✗
Bellani 2017	+	+	+	+	+
Shen 2019	+	+	+	+	+
Kamo 2019	+	-	-	+	-
Chan 2019	+	+	-	+	-
Chinh 2019	+	+	-	+	-
Fujishima 2020	+	+	-	+	-
Song 2020	+	+	-	+	-

Domains:
D1: Patient selection.
D2: Index test.
D3: Reference standard.
D4: Flow & timing.

Judgement
✗ High
- Some concerns
+ Low

Figure 2

Risk of bias assessment for individual studies.

Figure 3

Forest plots showing the sensitivity and specificity of the P/F ratio (cutoff 100) in the 18 included studies.

Figure 4

Forest plots showing the sensitivity and specificity of the P/F ratio (cutoff 100) in the 20 included studies.

Figure 5

Summary of the receiver-operating characteristic (SROC) curve with summary point estimates of sensitivity and specificity with 95% confidence intervals (CIs) for a P/F ratio of 100.

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 P/F ratio of 200.

Supplementary Files

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

- [Table1PF.xlsx](#)
- [Supplement1Protocol.docx](#)
- [Supplement2.docx](#)