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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Research

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Abstract

Background

PaO_2/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%).

Conclusion

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 PaO_2/FIO2 (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 fo*r *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

Study eligibility criteria

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

Data source and search method

We searched two electronic databases (MEDLINE and the Cochrane Central Register of Controlled Trials) for studies published before June 19, 2020. The search was conducted using the terms “respiratory distress syndrome,” “adult,” and “acute lung injury.” The details of the search strategy are reported in

Supplement 1. In the first phase, study data 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.

Discussion

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.

Conclusions

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

Abbreviations

ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID, coronavirus disease; DTA, diagnostic test accuracy; FP, false positive; FN, false negative; ICUs, intensive care units; P/F, PaO_2/FIO2; PRISMA, Preferred Reporting Items for a Systematic Review and Meta-analysis; QUADAS-2: Quality Assessment tool for Diagnostic Accuracy Studies-2; SROC: summary of receiver-operating characteristic; TP: true positive; TN: true negative.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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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. All authors approved the final draft and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

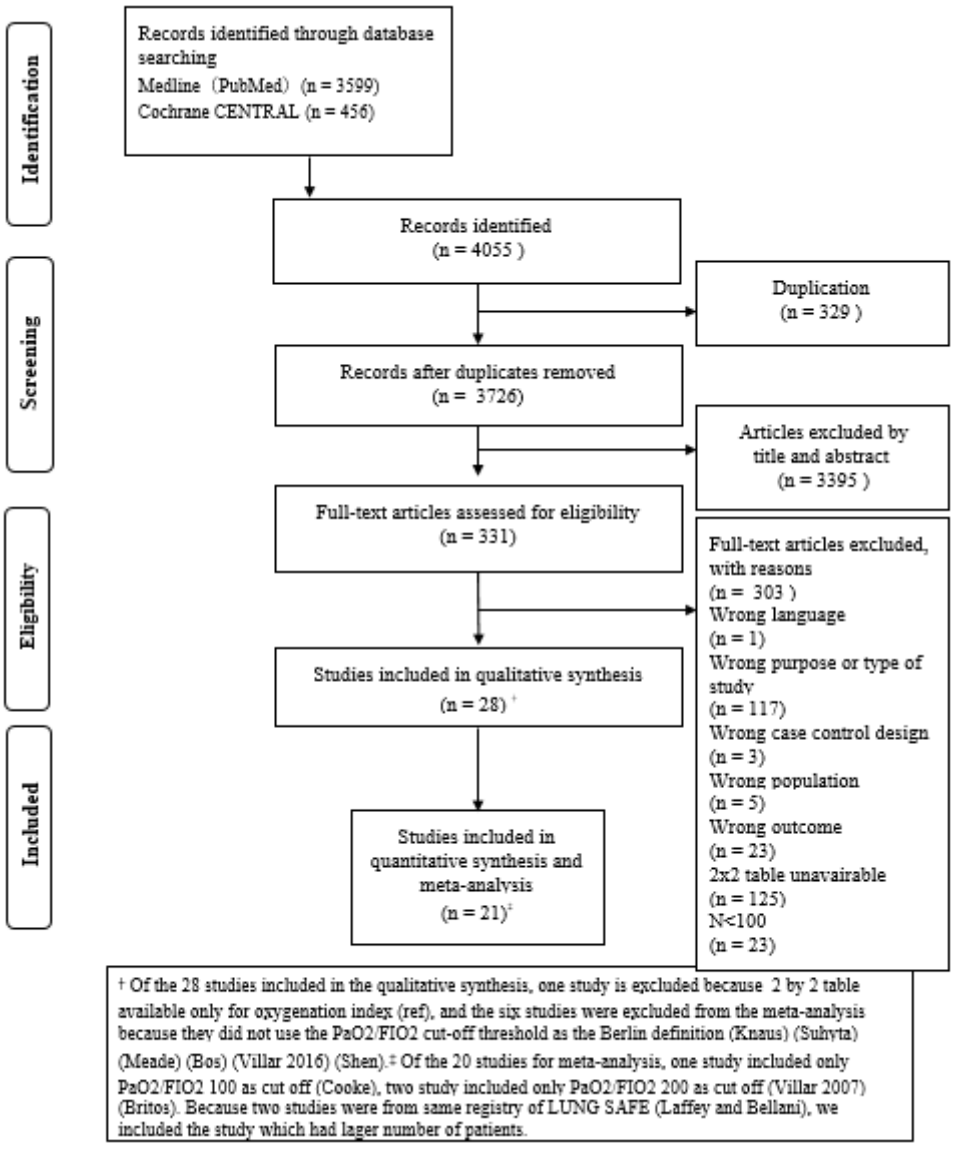

Figure 1

Flow diagram of the literature selection process.

Figure 2

Risk of bias assessment for individual studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kamo	22	18	20	93	0.52 [0.36, 0.68]	0.84 [0.76, 0.90]
Belleni	255	387	632	1539	0.29 [0.26, 0.32]	0.80 [0.78, 0.82]
Chawla	18	22	45	85	0.29 [0.18, 0.41]	0.79 [0.71, 0.87]
Laffey	257	297	696	1119	0.27 [0.24, 0.30]	0.79 [0.77, 0.81]
Villar	50	36	69	127	0.42 [0.33, 0.51]	0.78 [0.71, 0.84]
Lal	36	27	81	94	0.31 [0.23, 0.40]	0.78 [0.69, 0.85]
Ranieri	461	570	795	1844	0.37 [0.34, 0.39]	0.76 [0.75, 0.78]
Hernu	37	38	47	118	0.44 [0.33, 0.55]	0.76 [0.68, 0.82]
Choi	25	23	38	68	0.40 [0.28, 0.53]	0.75 [0.65, 0.83]
Neuschwander	223	103	416	262	0.35 [0.31, 0.39]	0.72 [0.67, 0.76]
DesPrez	25	71	53	179	0.32 [0.22, 0.44]	0.72 [0.66, 0.77]
Kallet	136	125	129	295	0.51 [0.45, 0.57]	0.70 [0.66, 0.75]
Fujishima	30	31	29	67	0.51 [0.37, 0.64]	0.68 [0.58, 0.77]
Song	59	33	44	65	0.57 [0.47, 0.67]	0.66 [0.56, 0.76]
Chen	31	61	54	92	0.36 [0.26, 0.48]	0.60 [0.52, 0.68]
Cooke	307	307	122	377	0.72 [0.67, 0.76]	0.55 [0.51, 0.59]
Chinh	42	25	31	28	0.58 [0.45, 0.69]	0.53 [0.39, 0.67]
Chan	44	112	17	90	0.72 [0.59, 0.83]	0.45 [0.38, 0.52]

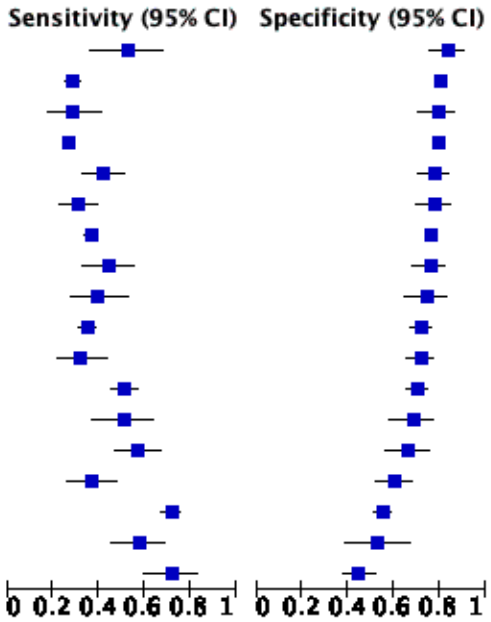

Figure 3

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

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chan	59	176	2	26	0.97 [0.89, 1.00]	0.13 [0.09, 0.18]
Chinh	69	45	4	8	0.95 [0.87, 0.98]	0.15 [0.07, 0.28]
Villar 2013	111	124	8	39	0.93 [0.87, 0.97]	0.24 [0.18, 0.31]
Fujishima	55	80	4	18	0.93 [0.84, 0.98]	0.18 [0.11, 0.27]
Kallet	242	349	24	70	0.91 [0.87, 0.94]	0.17 [0.13, 0.21]
Choi	57	75	6	16	0.90 [0.80, 0.96]	0.18 [0.10, 0.27]
Kamo	38	73	4	38	0.90 [0.77, 0.97]	0.34 [0.25, 0.44]
Song	90	80	13	18	0.87 [0.79, 0.93]	0.18 [0.11, 0.27]
Hernu	71	127	13	29	0.85 [0.75, 0.91]	0.19 [0.13, 0.26]
Bhadade	56	31	11	18	0.84 [0.73, 0.92]	0.37 [0.23, 0.52]
Chen	71	130	14	23	0.84 [0.74, 0.91]	0.15 [0.10, 0.22]
Britos	559	1221	116	415	0.83 [0.80, 0.86]	0.25 [0.23, 0.28]
Ranieri	1036	1815	220	599	0.82 [0.80, 0.85]	0.25 [0.23, 0.27]
Chawla	51	60	12	47	0.81 [0.69, 0.90]	0.44 [0.34, 0.54]
DesPrez	62	182	16	68	0.79 [0.69, 0.88]	0.27 [0.22, 0.33]
Lal	93	95	24	26	0.79 [0.71, 0.86]	0.21 [0.15, 0.30]
Villar 2007	45	54	12	59	0.79 [0.66, 0.89]	0.52 [0.43, 0.62]
Neuschwander	491	261	148	104	0.77 [0.73, 0.80]	0.28 [0.24, 0.33]
Bellani	670	1310	217	616	0.76 [0.73, 0.78]	0.32 [0.30, 0.34]
Laffey	703	955	250	461	0.74 [0.71, 0.77]	0.33 [0.30, 0.35]

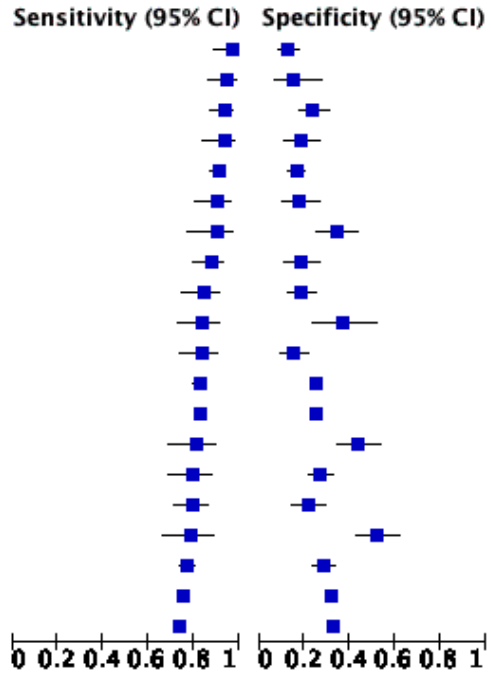

Figure 4

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

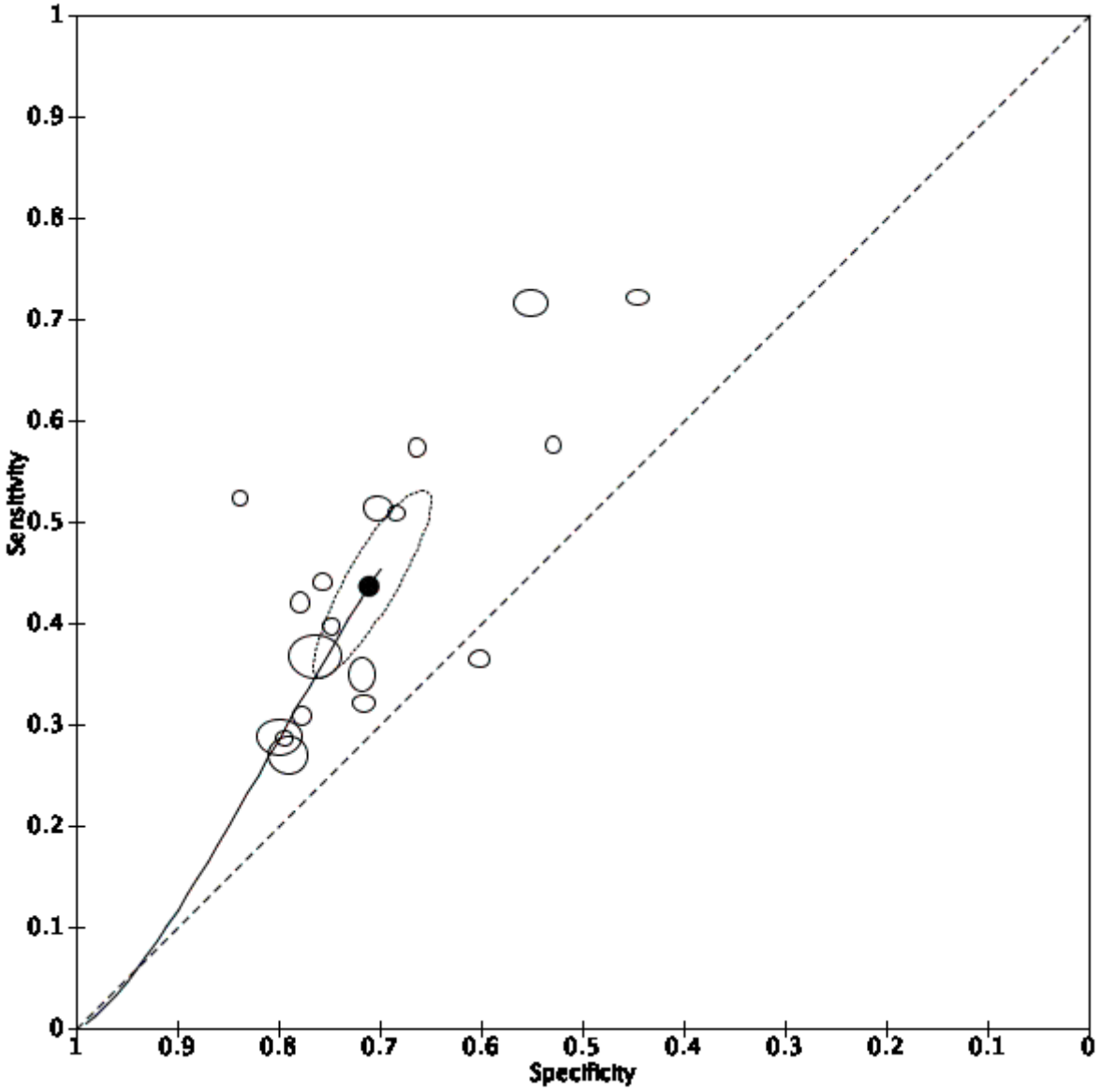

Figure 5

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.

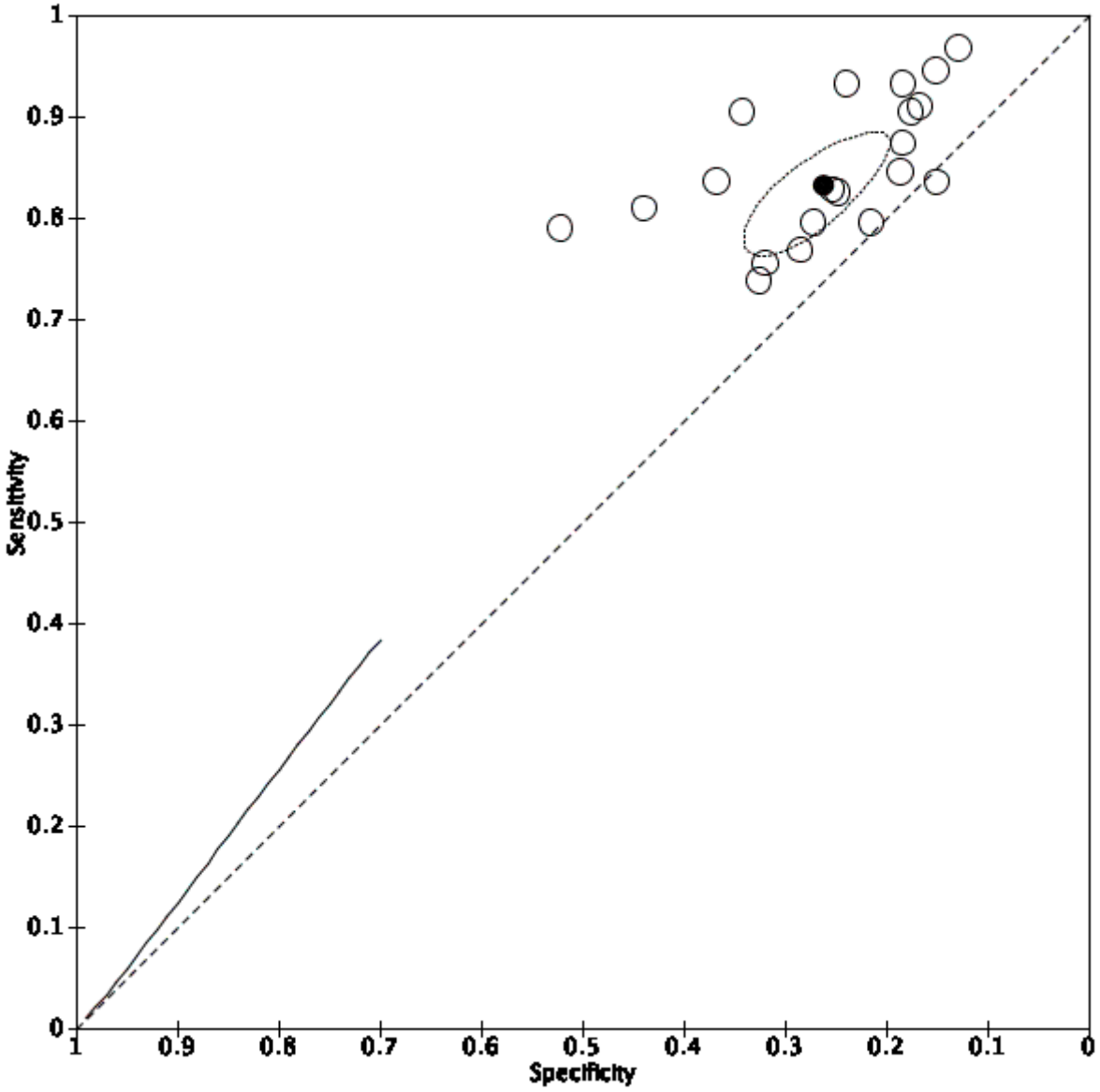

Figure 6

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