

# Meta-Analysis of Invasive versus Non-Invasive Techniques to Predict Fluid Responsiveness by Passive Leg Raising in the Critically Ill

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## Abstract

**Objective:** To analyze the accuracy and specificity of recent studies to compare the ability of predicting fluid responsiveness with Passive Leg Raising (PLR) by using invasive or non-invasive techniques during passive leg raising. **Data Sources:** MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were systematically searched. **Study Selection:** Clinical trials that reported the sensitivity, specificity and area under the receiver operating characteristic curve (AUC) between the responder and non-responder induced by passive leg raising and Volume Expansion (VE) in critical ill patients were selected. 246 studies were screened, 14 studies were included for data extraction, which met our inclusion criteria. **Data Extraction:** Data were abstracted on study characteristics, patient population, type and amount of VE, time of VE, definition of responders, position, techniques used for measuring hemodynamic change, number and percentage of responders, the correlation coefficient, sensitivity, specificity, best threshold and area under the ROC curve (AUC). **Meta-analytic techniques** were used to summarize the data. **Data Synthesis:** A total of 524 critical ill patients from 14 studies were analyzed. Data are reported as point estimate (95% confidence intervals). The pooled sensitivity and specificity of invasive techniques were 80% (73% - 85%) and 89% (84% - 93%) respectively with the area under the sROC of 0.94. While, the pooled sensitivity and specificity of non-invasive techniques were 88% (84% - 92%) and 91% (86% - 94%) respectively with the area under the sROC of 0.95. The pooled DOR of invasive techniques was 32.2 (13.6 - 76.8), which was much lower than that of non-invasive techniques with the value of 64.3 (33.9 - 121.7). **Conclusions:** The hemodynamic indexes changes induced by PLR could reliably predict fluid responsiveness. Non-invasive hemodynamic techniques with their accuracy and safety can benefit the daily work in ICUs. Because the num-

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ber of patients included in the present trials was small, further studies should be undertaken to confirm these findings.

## Keywords

Invasive, Non-Invasive, Fluid Responsiveness, Meta-Analysis

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## 1. Introduction

Fluid therapy is an essential part in Intensive Care Unit (ICU) to survive patients with hypovolemia. In fact, that's not easy. Studies have shown that about 50% of critically ill patients do not exhibit the desired effect [1]. How to assess intravascular volume accurately has been a critical problem.

Passive Leg Raising (PLR) is a reversible maneuver that mimics rapid Volume Expansion (VE) by shifting venous blood from the lower limbs toward the intrathoracic compartment [2]. Thus, PLR increases the cardiac preload. PLR has been validated to predict fluid responsiveness, but it requires the determination of CO or its surrogates with a fast-response device, because the hemodynamic changes may be transient [3] [4].

There are a lot of "fast-response devices" and all of them can be divided into 2 categories: invasive and non-invasive. Invasive hemodynamic techniques such as transpulmonarythermodilution (PiCCO), Vigileo, arterial BP transducer, pulmonary artery catheter are widely used in intensive units. Over the past few years, new techniques assessed for rapid and non-invasive prediction of fluid responsiveness have been introduced in clinical practice. Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), transthoracic Doppler ultrasonography (USCOM), Bioreactance technology-based system (NICOM), Continuous Non-invasive Arterial Pressure (CNAP) have been developed to predict fluid responsiveness.

Evidence shows that various studies have confirmed the ability of predicting fluid responsiveness by these techniques, but the predictive value of the hemodynamic response after PLR as a dynamic index of fluid responsiveness between invasive and non-invasive techniques has not been compared yet. The aim of this systematic review is to answer the question: can non-invasive techniques be better than invasive ones to be used as a tool for predicting volume responsiveness in critically ill during PLR maneuver and VE?

Data reporting conformed to the Standards for Reporting of Diagnostic Accuracy (STARD) [5].

## 2. Materials and Methods

### 2.1. Search Strategy

Two authors independently performed a search in MEDLINE (using PubMed as the search engine, from 1947), EMBASE (from 1974) and the Cochrane Database of Systematic Reviews for prospective studies in January 2014 with the following key words:

“Passive leg raising” AND (fluid therapy OR fluid responsiveness OR fluid expansion OR fluid load\* OR volume therapy OR volume responsiveness OR volume expansion).

## 2.2. Study Selection

Only full-text articles in indexed journals were included. Reviews, chapter, case reports, reference network and studies published in abstract form were excluded. No language restriction was imposed. We included only studies with patients admitted in intensive care unit (ICU). Children and pregnant women would be excluded. Articles were collected by one reviewer and crosschecked by another reviewer and references of included papers were examined to identify other studies of interest.

## 2.3. Inclusion Criteria

We included full-text studies with the following criteria: 1. PLR was performed and followed with VE; 2. the number of patients and boluses had been counted; 3. the reference standard of predicting fluid responsiveness had been described; 4. the number of responsive patients and non-responsive patients had been counted; 5. sensitivity, specificity and the threshold of the index in identifying those patients who subsequently responded to VE (responders) had been calculated.

## 2.4. Data Extraction and Quality Assessment

Data were extracted using a structured data collection sheet including the following items: authors, year of publication, study setting, population, age of patients, number of patients included, ventilation mode, cardiac rhythm (sinus vs. arrhythmias), type and amount of VE, time of VE, definition of responders, position, assessments used for measuring hemodynamic change, number of VE administered, number and percentage of responders, sensitivity, specificity, best threshold and area under the ROC curve (AUC). We use QUADAS-2 (quality assessment of diagnostic accuracy-2) [6] to assess the quality of included studies on diagnostic accuracy in systematic reviews. The checklist was structured with 4 parts: patient selection, index test, reference standard and flow and timing.

## 2.5. Statistical Analysis

We used RevMan 5.2 (Cochrane Collaboration, Oxford, UK) to make the QUADAS-2 scale to assess quality of studies on diagnostic accuracy to be included in systematic reviews. To calculate pooled values of sensitivity, specificity, diagnostic odds ratio (DOR) and area under summary receiver operating characteristic (sROC) curve we used MetaDiSC 1.4 (Unit of Clinical Biostatisticsteam of the Ramon y Cajal Hospital, Madrid, Spain). P-values of less than 0.05 were considered statistically significant. Publication bias was performed by STATA statistical software 12.0 (StataCorp, College Station, TX).

We used the Cochran Q statistic [7] to evaluate heterogeneity between studies. When the value of p less than or equal to 0.10 and  $I^2$  more than 50%, it could be regarded as

heterogeneity significantly and a random effect model was used to perform meta-analysis. For sensitivity and specificity, the Spearman correlation coefficient between those two parameters was calculated to evaluate a threshold effect determining heterogeneity [8].

For each study, sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), and DOR were calculated after constructing a  $2 \times 2$  contingency table. Pooled estimates with 95% confidence intervals (CIs) were calculated using a random-effects model. A summary receiver operating characteristic (sROC) curve was drawn according to the regression model proposed by Moses *et al.* [9] and it was performed to assess the interaction between sensitivity and specificity. The area under the sROC curve (AUC) was obtained to assess the diagnostic performance of hemodynamic techniques. Potential presence of publication bias was tested using the Egger [10] and Begg test [11].

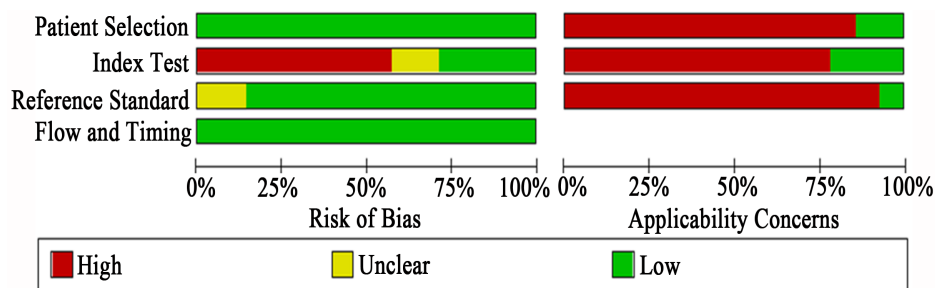
### 3. Results

#### 3.1. Process of Study Selection

The initial search yielded 246 articles after the first query in the three databases. Among them, 86 were excluded for not directly concerning item of interest. In the 160 full-articles, 103 were excluded because they were reviews, chapters or abstracts. 16 were excluded because they didn't perform PLR and another 14 were excluded because they didn't use VE. 13 were excluded because they didn't satisfy our inclusion criteria. Therefore, 14 studies [12]-[25] were included for final analysis.

#### 3.2. Characteristics of Included Studies

The clinical characteristics of the 14 included studies were summarized in **Table 1** and main results were reported in **Table 2** and **Table 3**. The results of QUADAS-2 were showed in **Figure 1**. All the included 14 studies were prospective studies with enrollment of patients with sign of inadequate tissue perfusion. We found good compliance with appropriate population selection, index test adequately described, appropriate reference standard, and adequate flow and timing. Population selection bias was minimized, as the inclusion criteria of the patients were close. However, no study described the blinding of the assessors to the outcome measurement of the results. 2 out of the 14 included studies didn't report the lasting time of PLR.



**Figure 1.** Results of QUADAS-2 (software RevMan 5.2).

**Table 1.** Main characteristics of the included studies.

Authors	Year	No.	Ventilation	Rhythm	VE	Position	Responder	Index	Techniques
Lafanechère [12]	2006	22	MV	sinus	500cc saline	supine position	$\Delta ABF \geq 15\%$	cABF-TEE cPP	TEE arterial BP transducer
Monnet [13]	2006	71	MV	sinus/arr	500cc saline	semi-recumbent	$\Delta ABF \geq 15\%$	cPP cABF-TEE	arterial BP transducer TEE
Lamia [14]	2007	24	MV/SB	sinus/AF	500cc saline	semi-recumbent	$\Delta SVI \geq 15\%$	cVTIAo-TTE cCO-TTE	TTE TTE
Maizel [15]	2007	34	SB	sinus	500cc saline	supine position	$\Delta CO-TTE \geq 12\%$	cCO-TTE cSV-TTE	TTE TTE
Thiel [16]	2009	89	MV/SB	sinus/arr	500cc saline, Ringer's lactate, HES	semi-recumbent	$\Delta SV \geq 15\%$	cSV-TTE	TTE(USCOM)
Monnet [17]	2009	34	MV	sinus/arr	500cc saline	semi-recumbent	$\Delta CI \geq 15\%$	cCI cPP	PiCCO arterial BP transducer
Biais [18]	2009	30	MV/SB	sinus	500cc saline	semi-recumbent	$\Delta SV-TTE \geq 15\%$	cSV cSV-TTE	Vigileo TTE
Préau [19]	2010	34	SB	sinus	500cc HES	semi-recumbent	$\Delta SV \geq 15\%$	cSV-TTE cPP	TTE arterial BP transducer
Guinot [20]	2011	17	MV	sinus/arr	500cc saline	semi-recumbent	$\Delta SV-TTE > 15\%$	cSV-TTE cCO-TTE	TTE TTE
Liu [21]	2011	20	MV	sinus/arr	250cc saline	semi-recumbent	$\Delta SV \geq 10\%$	cSV	PiCCO
Wang [22]	2011	33	MV/SB	sinus/arr	500cc saline	semi-recumbent	$\Delta SV-TTE \geq 15\%$	cSV-TTE cSV-USCOM	TTE USCOM
Monnet [23]	2012	39	MV	sinus	500cc saline	semi-recumbent	$\Delta CI \geq 15\%$	cPPV cPPV-CNAP	PiCCO CNAP
García [24]	2012	37	MV	sinus/arr	500cc HES	semi-recumbent	$\Delta CO \geq 15\%$	cCO-TEE cPP	TEE arterial BP transducer
Monnet [25]	2013	40	MV	sinus/arr	500cc saline	semi-recumbent	$\Delta CI \geq 15\%$	cCI	PiCCO

MV: mechanical ventilation, arr: arrhythmia, AF: atrial fibrillation, VE: volume expansion, min minutes, BP: blood pressure,  $\Delta$ : variation; c: PLR-induced changes, TTE: transthoracic echocardiography, TEE: transesophageal echocardiography, CI: cardiac index, CO: cardiac output, SV: stroke volume, PP: pulse pressure, PPV: pulse pressure variation, ABF: aortic blood flow, VTIAo: aortic velocity-time integral, USCOM: transthoracic Doppler ultrasonography, CNAP: continuous non-invasive arterial pressure.

**Table 2.** Pooled results for predictive capacity of invasive hemodynamic techniques.

Authors	Index	Boluses	TP	FP	FN	TN	AUC	Best Threshold	Sens.	Spec.	DOR	+LR	-LR
Lafanechère [12]	cPP	22	7	1	3	11	0.78	12	70	92	25.7	8.4	0.3
Monnet [13]	cPP	71	22	5	15	29	0.96	12	60	85	8.5	4	0.5
Monnet [17]	cCI	34	21	0	2	11	0.94	10	91	100	197.8	21.5	0.1
Biais [18]	cSV	30	20	2	0	8	0.96	13	100	80	139.4	4.3	0
Préau [19]	cPP	34	11	3	3	17	0.86	9	79	85	20.8	5.2	0.3
Liu [21]	cSV	46	12	2	3	29	0.85	12.5	80	93.5	58	12.4	0.2
Monnet [23]	cPPV	39	15	2	2	20	0.89	10	88	91	75	9.7	0.1
García [24]	cPP	37	14	3	7	13	0.73	11	67	81	8.7	3.6	0.4
Monnet [25]	cCI	40	20	1	1	18	0.98	15	95	95	360	18.1	0.1
Overall (95% CIs)		353							80	89	32.2	5.8	0.2
									(73 - 85)	(84 - 93)	(13.5 - 76.8)	(3.8 - 8.8)	(0.1 - 0.4)

TP: true-positive, FP: false-positive, FN: false-negative, TN: true-negative, AUC: area under the receiver operating characteristics curve, 95% CIs: 95% confidence intervals, Sens: sensitivity, Spec: specificity, DOR: diagnostic odds ratio, +LR: positive likelihood ratio, -LR: negative likelihood ratio, CI: cardiac index, SV: stroke volume, PP: pulse pressure, PPV: pulse pressure variation.

**Table 3.** Pooled results for predictive capacity of non-invasive hemodynamic techniques.

Authors	Index	boluses	TP	FP	FN	TN	AUC	Best Threshold	Sens.	Spec.	DOR	+LR	-LR
Lafanechère [12]	cABF-TEE	22	9	2	1	10	0.95	8	90	83	45	5.4	0.1
Monnet [13]	cABF-TEE	71	36	2	1	32	0.75	10	97	94	576	16.5	0
Lamia [14]	cVTIAo-TTE	24	10	0	3	11	0.96	12.5	77	100	69	18	0.3
Maizel [15]	cSV-TTE	34	15	3	2	14	0.9	8	88	83	35	5	0.1
Thiel [16]	cSV-TTE	102	38	4	9	51	0.89	15	81	93	53.8	11.1	0.2
Biais [18]	cSV-TTE	30	17	1	3	9	0.92	16	85	90	51	8.5	0.2
Préau [19]	cSV-TTE	34	12	2	2	18	0.94	10	86	90	54	8.6	0.2
Guinot [20]	cCO-TTE	25	11	2	2	10	0.87	5	85	83	27.5	5.1	0.2
Wang [22]	cSV-TTE	36	24	2	0	10	0.95	15	100	83.3	205.8	5.1	0
Monnet [23]	cPPV-CNAP	39	14	2	3	20	0.89	11	82	91	46.7	9.1	0.2
García [24]	cCO-TEE	37	20	1	1	15	0.97	12	95	94	300	15.2	0.1
Overall (95% CIs)		454							88	91	64.3	7.8	0.17
									(84 - 92)	(86 - 94)	(33.9 - 121.7)	(5.3 - 11.6)	(0.12 - 0.24)

TP: true-positive, FP: false-positive, FN: false-negative, TN: true-negative, AUC: area under the receiver operating characteristics curve, 95% CIs: 95% confidence intervals, Sens: sensitivity, Spec: specificity, DOR: diagnostic odds ratio, SV: stroke volume, ABF: aortic blood flow, VTIAo: aortic velocity-time integral, TTE: transthoracic echocardiography, TEE: transesophageal echocardiography, CNAP: continuous non-invasive arterial pressure.

A total of 524 patients were enrolled (range 17 - 89 for single paper) and a total of 574 VE were administered. The mean responder rate was 52.8%.

All studies were conducted in intensive care units (ICU) on patients with hypovolemia, whose attending physician decided to perform a fluid challenge. 2 study [15] [19] enrolled patients had spontaneous breathing without mechanical ventilator in sinus rhythm. The others [12] [13] [14] [16] [17] [18] [20]-[25] enrolled patients with mechanical ventilation and/or arrhythmias. The reference standard for definition of responders after fluid bolus as CO or its surrogates ranged between 10 and 15%. 11 out of 14 studies [12] [13] [14] [15] [17] [18] [20] [21] [22] [23] [25] used saline for volume expansion (VE). 2 studies [19] [24] used hetastarch for VE. Only 1 study used either saline, ringer's lactate or hetastarch for VE. PLR was starting from a supine position in 2 studies [12] [15], and from semi-recumbent position in 12 studies [13] [14] [16]-[25]. 9 studies [12] [13] [17] [18] [19] [21] [23] [24] [25] used invasive hemodynamic techniques like PiCCO, Vigileo and arterial BP transducer and 11 studies [12] [13] [14] [15] [16] [18] [19] [20] [22] [23] [24] used non-invasive techniques, such as TEE, TTE, NICOM, USCOM and CNAP.

### 3.3. Diagnostic Accuracy of Invasive Techniques

We first divided the 14 studies into 2 groups: invasive group [12] [13] [17] [18] [19] [21] [23] [24] [25] and non-invasive group [12] [13] [14] [15] [16] [18] [19] [20] [22] [23] [24]. Then we meta-analyzed all papers into each group. Results were reported in **Table 2** and **Table 3**. When a study used both invasive and non-invasive techniques

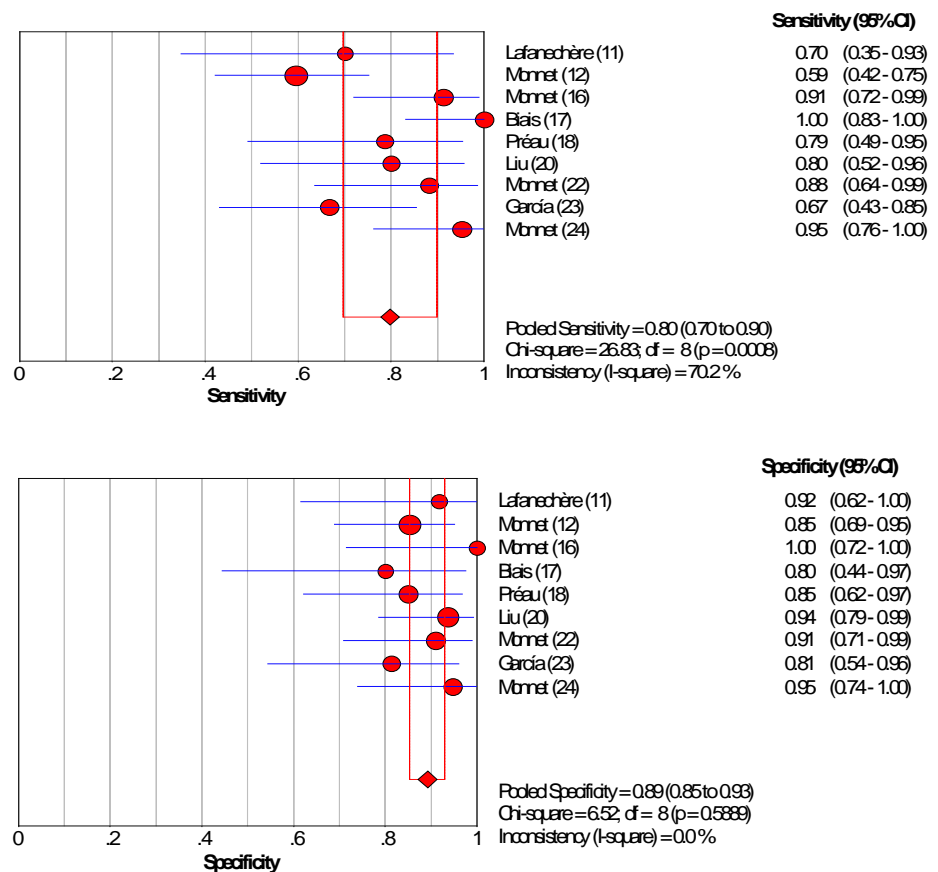
[12] [13] [18] [19] [23] [24], the indices of both techniques could be included. When a study reported analysis for two indices of the same category [14] [15] [17] [20] [21] [22] reported by the same technique only one was included in the meta-analysis in order to avoid duplication of sample size.

There were 9 papers (327 patients, 353 boluses) in the invasive group. The results  $I^2 = 39.6\%$  ( $<50\%$ ) and  $p = 0.1037$  ( $>0.05$ ) showed that heterogeneity was not significant among the trials. Forest plots of the pooled sensitivity and specificity were shown in **Figure 2**. The sensitivity ranged from 60% - 100% (pooled sensitivity 80%, 95% CI: 73% - 85%), while specificity ranged from 85% - 100% (pooled specificity 89%, 95% CI: 84% - 93%). DOR was 32.2 (95% CI: 13.5 - 76.8). Pooled values for positive likelihood ratio (+LR) and negative likelihood ratio (-LR) were 5.8 (95% CI: 3.8 - 8.8) and 0.2 (95% CI: 0.1 - 0.4). The threshold for predicting fluid responsiveness varied between 9% and 15%.

After excluded the threshold effect with spearman correlation coefficient = 0.233 and  $p = 0.546$  ( $>0.05$ ), we used Moses-Shapiro-Littenberg method to draw the symmetrical summary ROC curve (SROC) with AUC of 0.94.

### 3.4. Diagnostic Accuracy of Non-Invasive Techniques

There were 11 papers (430 patients, 454 boluses) in the non-invasive group. The results



**Figure 2.** Forest plots of pooled sensitivity between invasive and non-invasive techniques.

$I^2 = 0.0\%$  ( $<50\%$ ) and  $p = 0.809$  ( $>0.05$ ) showed that heterogeneity was not significant. Forest plots of the pooled sensitivity and specificity were shown in **Figure 3**. The sensitivity ranged from 77% - 100% (pooled sensitivity 88%, 95% CI: 84% - 92%), while specificity ranged from 83% - 100% (pooled specificity 91%, 95% CI: 86% - 94%). DOR was 64.3 (95% CI: 33.9 - 121.7). Pooled values for positive likelihood ratio (+LR) and negative likelihood ratio (-LR) were 7.8 (95% CI: 5.3 - 11.6) and 0.2 (95% CI: 0.1 - 0.2). The threshold for predicting fluid responsiveness varied between 5 and 15%.

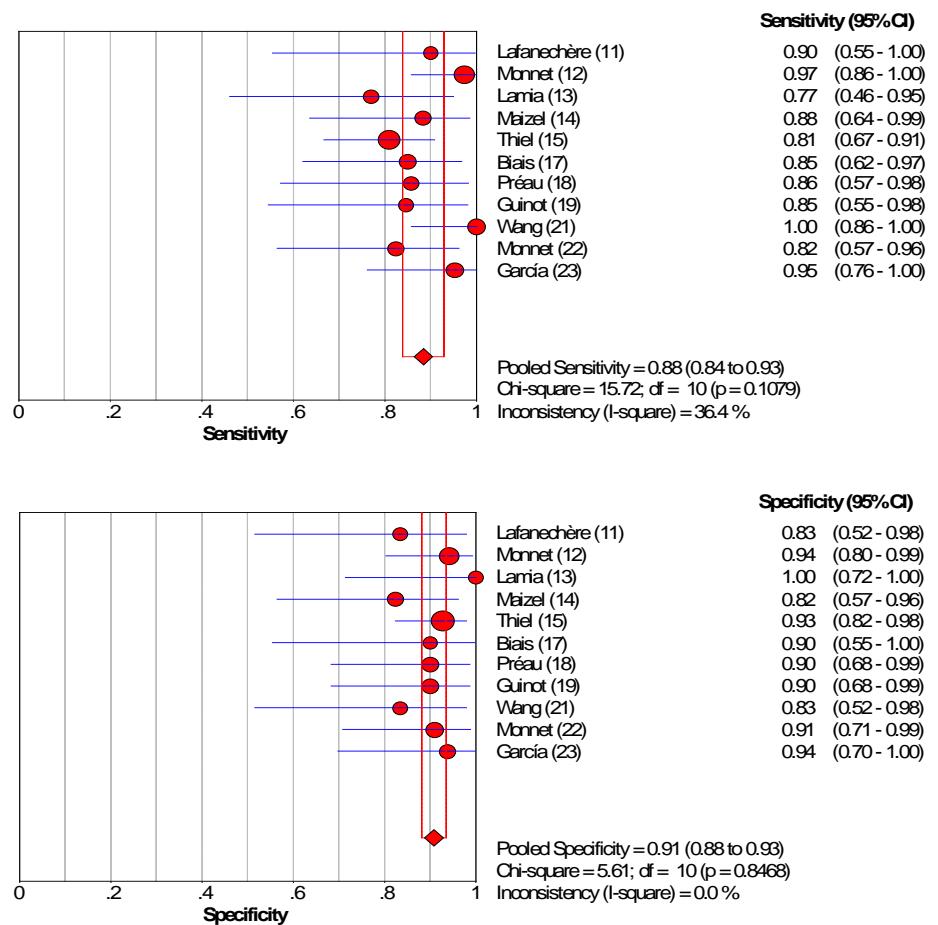
After excluded the threshold effect with spearman correlation coefficient = 0.361 and  $p = 0.276$  ( $>0.05$ ), we drew the symmetrical summary ROC curve (SROC) (**Figure 4**), with AUC of 0.95.

### 3.5. Publication Bias

The result of Egger test and Begg test showed that the potential publication bias was significant ( $P > 0.05$ ), which indicated a potential for publication bias.

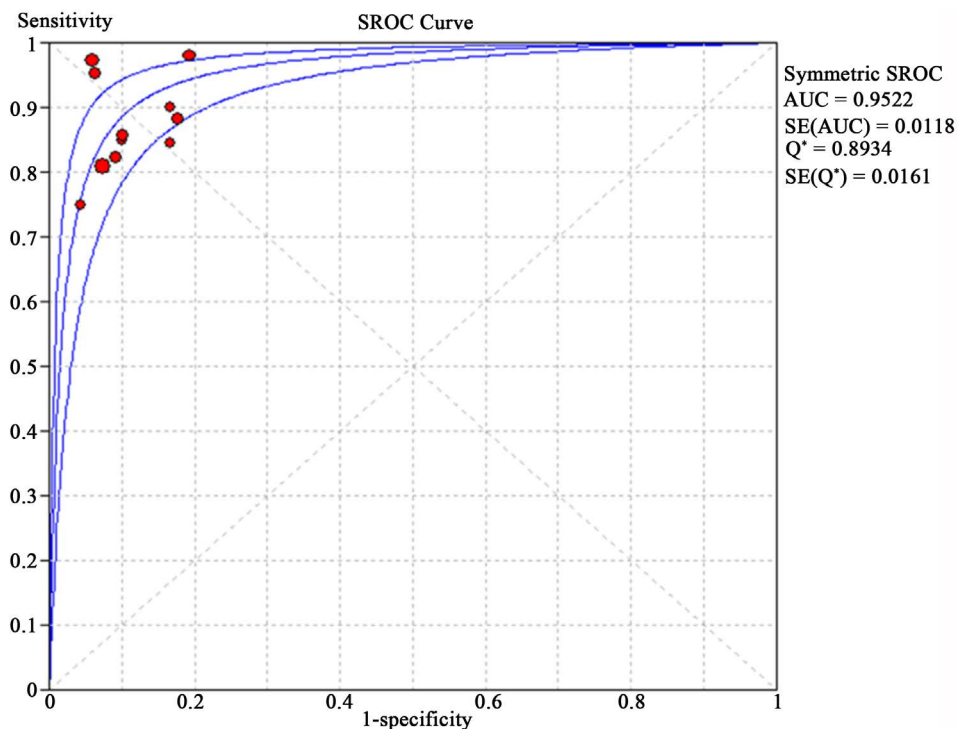
## 4. Discussion

The main finding of our systematic review are as follows: (1) The result of pooled sensi-



**Figure 3.** Forest plots of pooled specificity between invasive and non-invasive techniques.





**Figure 4.** Summary receiver operating characteristics curve for the ability of non-invasive techniques discriminate between responders and non-responders.

tivity and specificity between invasive and non-invasive techniques are 80% (73% - 85%) vs. 88% (84% - 92%) and 89% (84% - 93%) vs. 91% (86% - 94%), which cannot conclude inferior or superior; (2) The results of pooled DOR between invasive and non-invasive is 32.2 (13.6 - 76.8) vs. 64.3 (33.9 - 121.7), which indicate using non-invasive techniques have better discriminatory test performance with higher DOR values [8].

Knowing that dynamic indexes such as CO, CI, SV, ABF, SVV, PPV make use of provoked cardiac reaction assessed with fluid bolus and postural change can predict fluid responsiveness. A recent analysis by Vallee F shows that increase in thermodilution CO following a fluid bolus can predict fluid responsiveness [26]. The invasive techniques such as PiCCO, Vigileo, and arterial BP transducer are widely used in ICU to assess the patients' volume status. Also, a systematic review by Mandeville *et al.* [27] assessed the value of TTE in predicting fluid responsiveness in critically ill. In our review, both invasive and non-invasive hemodynamic techniques can accurately predict fluid responsiveness. DOR is the ratio of the odds of positive test results between the diseased and nondiseased groups. Non-invasive techniques have higher values of DOR can better discriminate test performance. Importantly, non-invasive techniques are much safer, more convenient than invasive ones. But the non-invasive techniques, especially for TTE and TEE require an experienced echocardiography practitioner, who can take echocardiography pictures to answer clinical questions arising in critical illness. Jensen showed that with only limited training, a diagnostic transthoracic window

was achieved 97 percent of the time when used in the evaluation of shock [28].

### Strengths and Limitations

The strengths of our meta-analysis lie in the methods adhering to recent guidelines for diagnostic reviews [6] [29] [30], as well as in the advanced statistical methods used [31], which analyze all reported thresholds, sensitivity, specificity and their correlated results simultaneously. Also no other review has compared the ability to predict fluid responsiveness between these 2 groups of hemodynamic techniques. The results of our review could guide the using of the techniques to assess patients' volume status in our clinical practice.

Limitations still exist in our meta-analysis. First, the pooling of diagnostic accuracy data inevitably contributed to sources of bias [7], which could be revealed in the significant amount of statistical heterogeneity across studies. Second, the number of patients included in the present trials was small (14 studies, 524 patients). A better review needs larger sample of studies. Third, the criteria of the included studies are based on clinical manifestation and the confounding factors such as cardiac function, respiratory function, severity of disease have not been analyzed.

### 5. Conclusion

The hemodynamic indexes induced by PLR can well discriminate between fluid responders and non-responders regardless of arrhythmia and ventilation mode. Non-invasive hemodynamic techniques with their accuracy and safety can benefit the daily work in ICUs.

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