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# Value of respiratory variation of aortic peak velocity in predicting children receiving mechanical ventilation: a systematic review and meta-analysis

Xiaoying Wang<sup>1\*†</sup>, Lulu Jiang<sup>2†</sup>, Shuai Liu<sup>3</sup>, Yali Ge<sup>1</sup> and Ju Gao<sup>1\*</sup>

## Abstract

**Background:** Accurate volume assessment is crucial in children under fluid therapy. Over the last decade, respiratory variation of aortic peak velocity ( $\Delta V_{Peak}$ ) has been applied in intensive care unit and surgeries to help clinicians guide fluid management. The aim of this systematic review and meta-analysis was to test diagnostic performance of  $\Delta V_{Peak}$  in predicting fluid responsiveness of ventilated children and to explore the potential factors that influence the accuracy of  $\Delta V_{Peak}$ .

**Methods:** We searched PubMed, Embase, and Cochrane from inception to April 2019 that evaluated association between  $\Delta V_{Peak}$  and fluid responsiveness after fluid challenge in children receiving mechanical ventilation. Data synthesis was performed within the bivariate mixed-effects regression model modified for synthesis of diagnostic test data.

**Results:** Eleven studies with a total of 302 pediatric patients were included in our meta-analysis. The pooled sensitivity and specificity of  $\Delta V_{Peak}$  was 0.89 (95%CI = 0.77 to 0.95) and 0.85 (95%CI = 0.77 to 0.91), respectively. The diagnostic odds ratio (DOR) of  $\Delta V_{Peak}$  was 48 (95%CI = 15 to 155). SROC yielded an area under the curve of 0.91 (95%CI = 0.88–0.93). The  $\Delta V_{Peak}$  cutoff value was nearly conically symmetrical distribution and varied from 7 to 20%. After excluding several extreme studies, most data were centered between 12 and 13%. The median and mean cutoff values of  $\Delta V_{Peak}$  were 12.2% and 12.7%, respectively. In subgroup analysis, compared to total data analysis,  $\Delta V_{Peak}$  performed weaker in the younger children group (mean ages < 25 months), with lower area under the summary receiver operating characteristic curve (AUSROC) of 0.80 (0.76 to 0.83), but stronger in the older children group (mean ages > 25 months), with AUSROC of 0.96 (0.94 to 0.97).

**Conclusions:** Overall,  $\Delta V_{Peak}$  has a good ability in predicting fluid responsiveness of children receiving mechanical ventilation, but this ability decreases in younger children (mean age < 25 months). The optimal threshold of  $\Delta V_{Peak}$  to predict fluid responsiveness in ventilated children is reliable between 12 and 13%.

**Trial registration:** The study protocol was registered prospectively on PROSPERO no. [CRD42019129361](https://doi.org/10.1186/1745-2974-4-29361).

**Keywords:** Aortic, Pediatric, Velocity, Fluid, Ventilation

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## Background

Fluid resuscitation is the cornerstone of fluid management wherever in ICU or in perioperative period. Excessive volume expansion increases the risk of pulmonary edema, impairs the cardiac ventricular function, and even causes renal dysfunction [1]. However, hypovolemia could also lead to oxygen delivery disorder in critical organs which poses a great threat to life [2, 3].

Different from adult patients, pediatric patients possess larger ratio of body surface area to weight and higher water quality. Physically, children's body compositions such as water proportion or muscle proportion are changing as they grow older, especially rapidly changing in preterm and term infants during the first 12 months of life [4]. Moreover, the myocardial structure of the heart, particularly the volume of cellular mass devoted to contractility, is significantly less developed in neonates than in adults. These differences, as well as developmental changes in contractile proteins, produce a leftward displacement of the cardiac function curve and less compliant ventricles. This developmental immaturity of myocardial structures also accounts for the tendency toward bi-ventricular failure, sensitivity to volume loading, poor tolerance of increasing afterload, and heart rate-dependent cardiac output [5, 6]. Due to pediatric patients' special physical body structure, those deleterious effects caused by inappropriate fluid therapy should be taken more seriously in children. Therefore, physicians need to make a prompt and precise clinical decision in preloading judgment for children.

Considering special physical structure, it is hard to accurately assess children volume state in many situations. Clinically, many monitoring indices are applied to help physicians to assess fluid responsiveness. Traditional static indices, such as blood pressure (BP), central venous pressure (CVP), and pulmonary artery wedge pressure (PAWP), although are important but of limited sensitivity and specificity, especially in intra-abdominal hypertension, one lung ventilation, and prone position [7–9]. The famous Frank–Starling Law mandates that, in a certain range capability, the heart could adjust ventricular contractility and cardiac ejection to dynamic changes in ventricular filling [10, 11]. According to this, usually, a patient, who has the increment over 15% or 10% from baseline measurements in physiological parameters after volume expansion, is defined as fluid responsiveness positively [12–14]. Usually, indices which are directive to reflect cardiac ejection, such as stroke volume (SV), cardiac output (CO), cardiac index (CI), were seen as the gold standard indices to judge fluid responsiveness [14]. However, the measurement of the gold standard indices needs invasive operation and expensive monitoring equipments although they are accurate. Over the last decade, hemodynamic parameters,

such as stroke volume variation (SVV) or pulse pressure variation (PPV), were reported to have a strong capability to assess fluid responsiveness during ventilation [15–17]. These hemodynamic parameters are based on heart-lung interaction that, in the air-tight thoracic construction, mechanical ventilation introduces cyclic changes in preload, leading to matched cardiac ejection and pulse pressure variation [18, 19]. However, the expensive equipment and invasive procedure also restrict the widespread application of these parameters.

Recently, noninvasive dynamic indices that calculate variation of peak velocity of the artery during several respiratory cycles measured by ultrasound have become an alternative quick volume assessment method [20, 21]. However, vessels in pediatric patients are thinner and more variable than adults. These distinctions bring challenges to noninvasive ultrasonographic techniques in children. Among all the vessels, the aortic artery is the largest and the nearest vessel next to cardiac ejection and is feasible and available to access whenever in ICU or in operating room. A recent review has reported that only respiratory variation in aortic blood flow peak velocity ( $\Delta V_{Peak}$ ) has the capability to predict fluid responsiveness in children rather than SVV or PPV [22]. In 2015, a meta-analysis of 6 studies concluded that  $\Delta V_{Peak}$  showed good diagnostic accuracy in ventilated children [23]. However, it failed to find the optimal  $\Delta V_{Peak}$  threshold and potential factors that influence the accuracy of  $\Delta V_{Peak}$  due to limited included studies.

Our research was conducted to estimate the diagnostic accuracy of  $\Delta V_{Peak}$  as a predictor of fluid responsiveness in ventilated children, explore the potential factors that influence the accuracy of  $\Delta V_{Peak}$ , and analyze the most accurate threshold of  $\Delta V_{Peak}$  to predict fluid responsiveness in ventilated children.

## Methods

### Study selection and inclusion criteria

All diagnostic tests that study  $\Delta V_{Peak}$  as a predictor of fluid responsiveness of ventilated children were included in our research. The gold standard method of assessing fluid responsiveness was defined as an increase in CO, CI, SV, and stroke volume index (SVI) after volume expansion. And the sensitivity, specificity, and cutoff value of  $\Delta V_{Peak}$  to predict fluid responsiveness in ventilated children could be found or calculated in the original work.

Studies which did not clarify the patients' age, number and basic characteristics, original paper or effective data unavailable, spontaneously breathing patients, studies conducted in animals or experimental researches, reviews, and letters were excluded. No language restriction was applied. No ethical and patient consent was required.

### Search strategy and data extraction

Two authors searched relevant clinical studies on PubMed, Embase, and Cochrane from inception to April 2019, and then independently screened literature, extracted data, and evaluated quality. If discrepancy existed, it was solved by the third arbitration. The whole search strategy used free words including fluid, responsiveness, pediatric, children, infant, kid, child, aortic, peak, and variation, and we combined words or phrases freely once more to acquire thorough results.

All the search was implemented by two authors strictly under the protocol, both of them screened the title and abstract. Irrelevant papers were neglected, while relevant and directly related papers were searched for full text, and those studies that measured  $\Delta V_{Peak}$  as the secondary observational index rather than the main index or the only index might also be included. Non-English language research was looked for original resources. Extracted data included three parts: the first one was basic information about the research such as the number of patients and study year. The second and the most important part was the results of the gold standard index and study index, including the gold standard index and the assessment of fluid responsiveness, cutoff value, sensitivity, specificity, and the area under receiver operating characteristic curve (ROC) of  $\Delta V_{Peak}$ . According to the collected data, we calculated true positive, false positive, false negative, and true negative values to construct the  $2 \times 2$  contingency table. The last one was discrepancy among studies that could be the heterogeneity or potential factors that influence  $\Delta V_{Peak}$ . We collected age, liquid sort, measuring tool, ventilation parameter, vasoactive drugs, and study places.

All included researches were needed to provide adequate information satisfying meta-analysis. If data was unclear in the original paper to form  $2 \times 2$  contingency table or characteristic form, we sent emails to the corresponding author for clarifying. If the author failed to respond in 1 month, we excluded the study in the final analysis.

### Quality assessment

Included studies were assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) recommended by the Cochrane Handbook [24, 25]. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. All domains were evaluated in terms of risk of bias and would be answered as “yes,” “no,” and “unclear” according to the specific content of each domain. The risk could be defined as low under the circumstance of a consistency of “yes,” and if all questions’ answers were “yes” but only one was “no,” the bias was possibly existing, and the author needs to judge the risk level

according to the guidelines. “Unclear” was defined if the original study failed to provide adequate information that the authors had difficulty to judge. Quality assessment was performed by Revman software 5.3.

### Statistical analysis

Data synthesis was performed within the bivariate mixed-effects regression model that could incorporate the negative correlation, which might arise between the sensitivity and specificity as a result of the different threshold value of  $\Delta V_{Peak}$  used in studies [26, 27]. We estimated overall pooling of sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence interval (CI) using a bivariate random-effects model. We also plotted summary receiver operating characteristic curve (SROC) and calculated the area under the summary receiver operating characteristic curve (AUSROC).

Scatter plot was conducted to observe the distribution, dispersion, central tendency, and extremum of  $\Delta V_{Peak}$  cutoff value in all included studies. Mean and median  $\Delta V_{Peak}$  cutoff values were also calculated. We finally combined the mean, median, and scatter plot to estimate the optimal  $\Delta V_{Peak}$  threshold value for the prediction of fluid responsiveness in ventilated children.

Heterogeneity was quantitatively assessed by using the chi-square test and Cochran’s  $Q$  test. To describe the percentage of total attributed to heterogeneity rather than chance, we quantified the effect of heterogeneity using inconsistency ( $I^2$ ).  $P$  value for  $Q$  test  $< 0.1$  or  $I^2 > 50\%$  were considered existing significant heterogeneity. Heterogeneity caused by the threshold effect in the diagnostic test was calculated in the Spearman correlation coefficient, which was estimated by the Moses–Shapiro–Littenberg [28]. Meta-regression was conducted to explore the potential sources of heterogeneity among studies beyond the threshold effect. Age, gold standard indices, fluid types, and vasoactive drugs were considered as potential factors to discriminate subgroups.

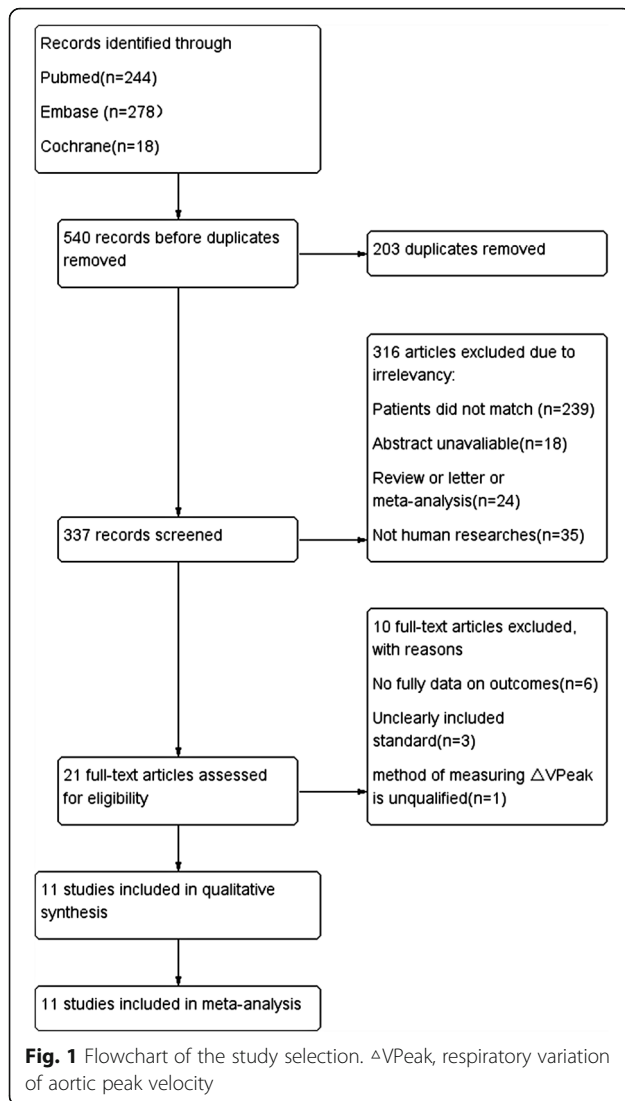
Public bias was estimated by Deek’s funnel plot asymmetry test, with  $P < 0.1$  indicating statistical significance [29].

The results were expressed as mean (95%CI) or as mean  $\pm$  standard deviation. Meta-analysis was performed by Stata 15.0 (StataCorp, College Station, TX) with the Midas module. A two-tailed  $P < 0.05$  was considered statistically significant.

## Results

### Characteristic of studies

Our meta-analysis yielded 540 studies after initially reviewed in three databases. Figure 1 shows the PRISMA selection of this meta-analysis. A total of 203 studies were removed due to duplicates. In the remaining 337 studies, 316 were excluded because of patients not eligible for the study purpose, abstract unavailable, reviews



or letters, and animal researches. Further screening the full article, 10 full texts were excluded due to incomplete outcomes, unclearly included standard, and unqualified method of measuring  $\Delta V_{Peak}$ . Finally, 11 studies with a total of 302 pediatric patients were included in our meta-analysis [30–40].

Characteristics of the included studied are summarized in Tables 1 and 2. A total of 161 children patients were responders (53.3%) to fluid challenge. The cutoff value of  $\Delta V_{Peak}$  varied from 7 to 20%. Ten studies were performed before, during, or after cardiac surgery ( $n = 4$ ) or neurosurgery ( $n = 3$ ), and two of them took measurement time point after arriving at ICU for 30 min [35] and 1 h [31]. However, only one study [30] was performed in ICU with mixed diseases in critically ill children. Four studies referred  $\Delta SV > 15\%$ , and five studies referred  $\Delta SVI > 15\%$  as the gold standard index of responders to fluid challenge. Except Favia et al. [38], all

other included studies were prospective diagnostic tests, and the gold standard index in this study was measured by peripheral artery wave contour analysis monitor rather than ultrasound.  $\Delta V_{Peak}$  in the total 11 studies was all performed with transthoracic echocardiography ( $n = 7$ ) or transoesophageal echocardiography ( $n = 4$ ).

### Methodological quality of studies

All included studies met patient spectrum criteria, had acceptable delays between index and reference tests, and performed the index and reference test in all included patients. One study used MostCare™ monitor to measure CI as a reference standard. Overall, the included studies were poorly reported in terms of blindness between index and reference tests, and most studies clarified uninterpretable tests unclearly. Table 3 and Fig. 2 show the methodological quality of the included studies, which was assessed by QUADAS2.

### Prediction of fluid responsiveness based on $\Delta V_{Peak}$

Pooled sensitivity of  $\Delta V_{Peak}$  was 0.89 (95%CI 0.77 to 0.95), and pooled specificity of  $\Delta V_{Peak}$  was 0.85 (95%CI 0.77 to 0.91), presented in Fig. 3. The positive and negative likelihood ratio of  $\Delta V_{Peak}$  was 5.9 (95%CI 3.6 to 9.7) and 0.12 (95%CI 0.05 to 0.29), respectively. The diagnostic odds ratio (DOR) of  $\Delta V_{Peak}$  was 48 (95%CI 15 to 155). SROC yielded an area under the curve of 0.91 (95%CI 0.88–0.93), presented in Fig. 4.

### The assessment optimal $\Delta V_{Peak}$ threshold value to predict fluid responsiveness in ventilated children

The  $\Delta V_{Peak}$  cutoff value in each included studies is presented in a scatter plot shown in Fig. 5. In Fig. 5, the  $\Delta V_{Peak}$  cutoff values were nearly conically symmetrical distribution, varied from 7 to 20%, and excluding several extreme studies, most data were centered between 12 and 13%. The mean  $\Delta V_{Peak}$  cutoff value was 12.7%, with the deviation of 0.03. The medium  $\Delta V_{Peak}$  cutoff value was 12.2%.

### Heterogeneity investigation

Heterogeneity of these studies was assessed with Cochran's  $Q$  of 1.98 and overall  $I^2$  statistic of 0%. No significant heterogeneity was found for specificity, DOR, and positive and negative likelihood ratio. However,  $I^2$  statistic of sensitivity was 62.23% and Cochran's  $Q$  of it was 26.27. The cutoff value of  $\Delta V_{Peak}$  varied from 7 to 20%, which could cause threshold effect heterogeneity. The Spearman correlation coefficient was 1, indicating that the proportion of heterogeneity likely due to the threshold effect was 100%. As a result, meta-regression was unnecessary.

**Table 1** Selected characteristics of the included studies

No.	Authors/year	Sample size	Age (months)	Settings or time point of measure	VE	Golden index (responders)	Tool measuring golden index	Tool measuring $\Delta V_{Peak}$	Tide volume (ml/kg)	PEEP (cmH <sub>2</sub> O)	Vasoactive drugs
1	Durand 2008	26	M = 28.5	ICU	20 ml /kg/6%HES or saline 15–30 min	$\Delta SV > 15\%$	TTE	TTE	7.4	4	Yes
2	Choi 2010	21	A = 30	VSD repair, 1 h after arriving at ICU	10 ml/ kg/6%HES over 20 min	$\Delta SV > 15\%$	TTE	TTE	10	0	Yes
3	Renner 2011	27	A = 17	Before cardiac surgery begin	10 ml/ kg/6%HES	$\Delta SVI > 15\%$	TOE	TOE	10	3–5	Yes
4	Pereira 2011	30	A = 112	Before neurosurgery incision	20 ml /kg/saline over 15 min	$\Delta VTI > 15\%$	TTE	TTE	10	0–2	Yes
5	Byon 2013	33	A = 72.1	Stable during neurosurgery	10 ml/ kg/6%HES 10 min	$\Delta SVI > 10\%$	TTE	TTE	10	0	UC
6	Lee 2014	26	A = 28	VSD repair, 30 min after arriving at ICU	10 ml/ kg/6%HES 20 min	$\Delta SV > 15\%$	TTE	TTE	10	5	Yes
7	Lee 2015	29	A = 13.7	Once sternum closed after VSD repair	10 ml/ kg/6%HES 10 min	$\Delta SVI > 15\%$	TOE	TOE	10	UC	Yes
8	Krishna 2016	42	A = 76	General endotracheal anesthesia	10 ml/ kg/1%DRL 5-10 min	$\Delta SVI \geq 15\%$	TTE	TTE	10	0	UC
9	Favia 2017	16	A = 24.2	Sternal closure in cardiac surgery	10 ml /kg/ crystalloid or blood products	$\Delta CI > 10\%$	MostCare™	TOE	8–10	0–10	No
10	Lee 2017	30	A = 19.2	After cardiac surgery end before entering ICU	10 ml/ kg/6%HES 20 min	$\Delta SVI > 15\%$	TOE	TOE	10	UC	Yes
11	Morparia 2018	22	A = 69.8	Neurosurgery	10 ml/ kg/ crystalloid	$\Delta SV > 15\%$	TTE	TTE	8–10	0–4	sNO

A average age, *min* minute, M median age, VE volume experiment, HES hydroxyethyl starch, DRL dextrose Ringer's lactate,  $\Delta V_{Peak}$  respiratory variation of aortic peak velocity, VSD ventricular septal defect, PEEP positive end-expiratory pressure, UC unclear, SV stroke volume, SVI stroke volume index, VTI velocity-time integral, TTE transthoracic echocardiography, TOE transoesophageal echocardiography

**Table 2** Diagnostic performance of pulse pressure variation from included studies

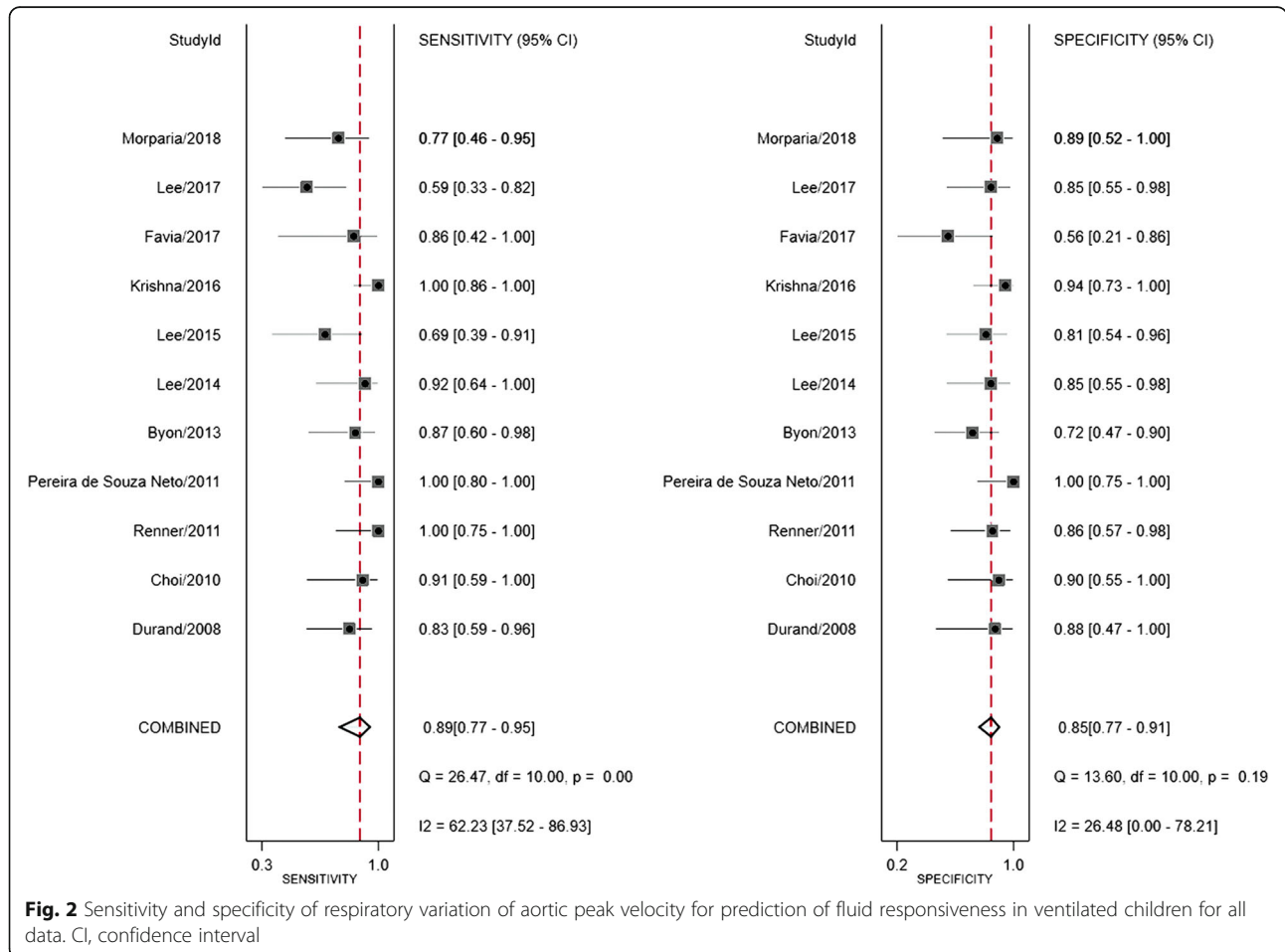
No.	Authors/year	Threshold <sup>a</sup> (%)	TP	FP	FN	TN	Sens (%)	Spec (%)	AUROC	Responders (%)
1	Durand 2008	12	15	1	3	7	81.2	85.7	0.85	69.23
2	Choi 2010	20	10	1	1	9	91	90	0.83	52.38
3	Renner 2011	7	13	2	0	12	100	85	0.92	48.15
4	Pereira 2011	10	17	0	0	13	100	100	1.0	56.67
5	Byon 2013	11	13	5	2	13	86.7	72.2	0.804	45.45
6	Lee 2014	14	12	2	1	11	92.0	85.0	0.956	50.00
7	Lee 2015	13.5	9	3	4	13	69.2	78.6	0.77	44.83
8	Krishna 2016	12.2	24	1	0	17	100	94	0.975	57.14
9	Favia 2017	16.5	6	4	1	5	83.0	55.0	0.70	43.75
10	Lee 2017	12	10	2	7	11	58.8	84.6	0.765	56.67
11	Morparia 2018	12.3	10	1	3	8	77	89	0.90	59.09

TP true positive, FP false positive, FN false negative, TN true negative, Sens sensitivity, Spec specificity, AUROC area under the receive operator characteristic curve, Threshold<sup>a</sup> threshold used in studies to achieve corresponding sensitivity and specialty, 95%CI 95% confidence interval

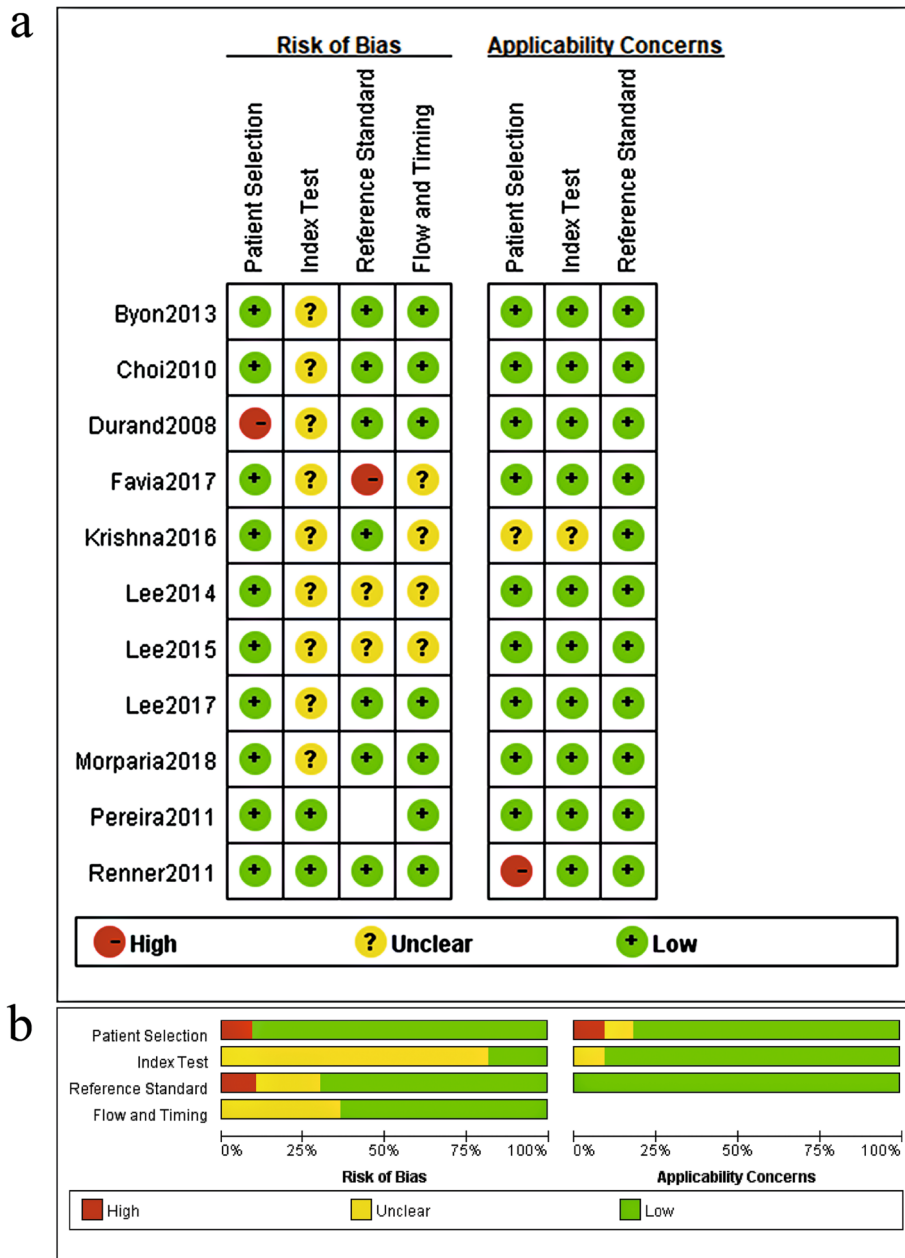
**Table 3** Quality assessment of included studies using QUADAS-2 domains

Author/year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Durand 2008	☹	?	☺	☺	☺	☺	☺
Choi 2010	☺	?	☺	☺	☺	☺	☺
Renner 2011	☺	☺	☺	☺	☹	☺	☺
Pereira 2011	☺	☺	☺	☺	☺	☺	☺
Byon 2013	☺	?	☺	☺	☺	☺	☺
Lee 2014	☺	?	?	?	☺	☺	☺
Lee 2015	☺	?	?	?	☺	☺	☺
Krishna 2016	☺	?	☺	?	?	?	☺
Favia 2017	☺	?	☹	?	☺	☺	☺
Lee 2017	☺	?	☺	☺	☺	☺	☺
Morparia 2018	☺	?	☺	☺	☺	☺	☺

☺ low risk, ☹ high risk, ? unclear risk



**Fig. 2** Sensitivity and specificity of respiratory variation of aortic peak velocity for prediction of fluid responsiveness in ventilated children for all data. CI, confidence interval



**Fig. 3** Risk of bias and applicability concerns for the studies included in the meta-analysis. **a** Risk-of-bias summary. **b** Risk-of-bias graph

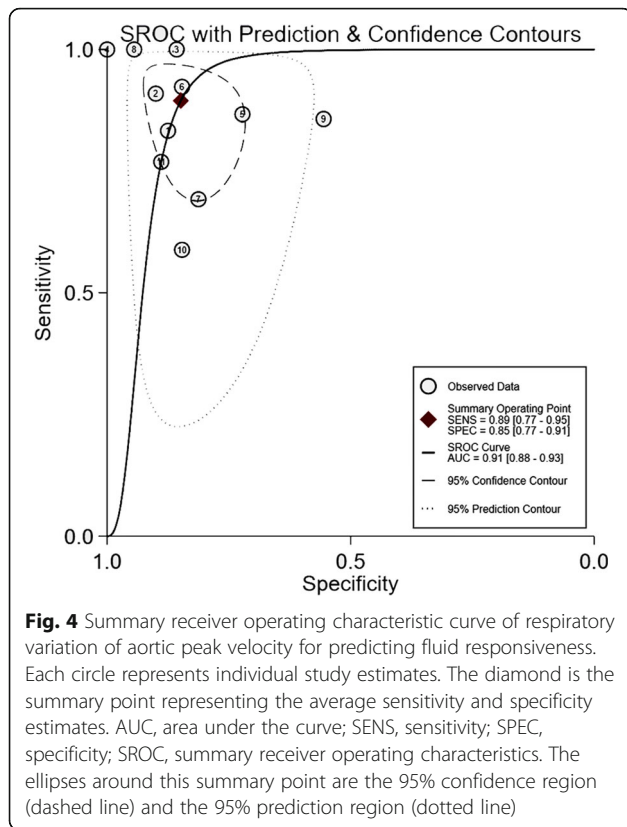
**Subgroup analysis**

In subgroup analysis, we found that  $\Delta$ VPeak performed weak in the younger children group, with the area under the curve of ROC of only 0.77, 0.70, and 0.765 in mean age of 13.7 months [36], 24.2 months [38], and 19.2 months [39], respectively. Compared to the total data, the younger children group (mean ages < 25 months) had lower AUSROC of 0.80 (0.76 to 0.83). However,  $\Delta$ VPeak performed a stronger ability of prediction in the older children group (mean ages > 25 months), with

AUSROC of 0.96 (0.94 to 0.97), presented in Table 4 and Fig. 6. Besides, the prediction accuracy of  $\Delta$ VPeak was not affected by the gold standard index, vasoactive drugs, and fluid types (see Additional file 1).

**Public bias**

Deek’s funnel plot asymmetry test of  $\Delta$ VPeak is shown in Fig. 7, and no significant public bias was found in our meta-analysis ( $P = 0.12$ ).

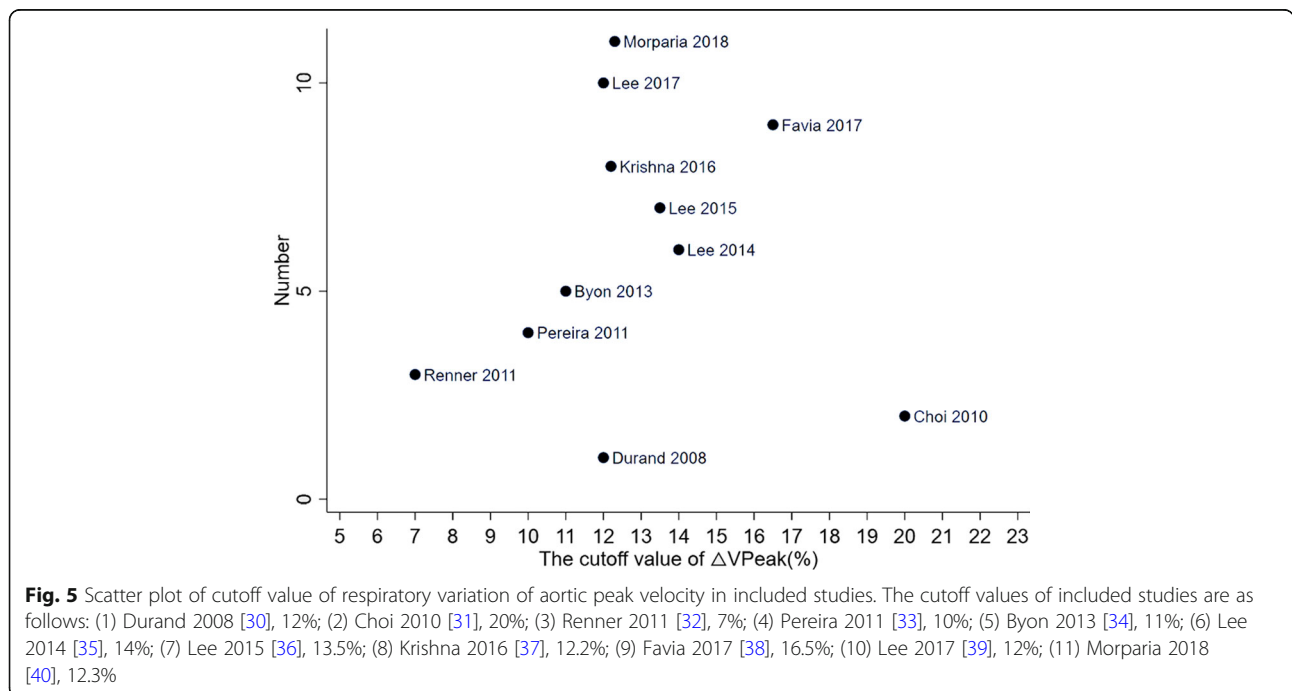


### Discussion

Our systematic review and meta-analysis found that overall,  $\Delta V_{Peak}$  performed well in predicting fluid responsiveness of ventilated children, with pooled sensitivity of 0.85, pooled specificity of 0.89, and AUSROC of 0.91. We synthesized the mean, median, and scatter plot to estimate that the most accurate value of  $\Delta V_{Peak}$  for prediction of fluid responsiveness in ventilated children is reliable between 12 and 13%. However, the accuracy of  $\Delta V_{Peak}$  decreased in children less than 25 months.

As we all know, each cardiac contraction brings a stroke volume from the left ventricle, and the blood flow passes through the vessel tract at different speed depending on the amount of blood ejection, the diameter of the tract, and blood velocity. In fact,  $\Delta V_{Peak}$  measured by ultrasound is similar to SVV, but it transforms invisible stroke volume to digital speed as an alternation. According to Rudnick's theory, the closer the measurement position to cardiac ejection, the more accurate the prediction for hemodynamic indices to reflect central perfusion [41]. In our study,  $\Delta V_{Peak}$  showed a strong ability to predict fluid responsiveness in ventilated children, with AUSROC more than 0.9 and high sensitivity and specificity.

Desgranges et al. [23] first performed a six study systematic review and meta-analysis, but it failed to find optimal threshold value for  $\Delta V_{Peak}$  to predict fluid responsiveness in ventilated children due to extent variation of  $\Delta V_{Peak}$  cutoff value and inadequate data. However, more studies were published in the recent





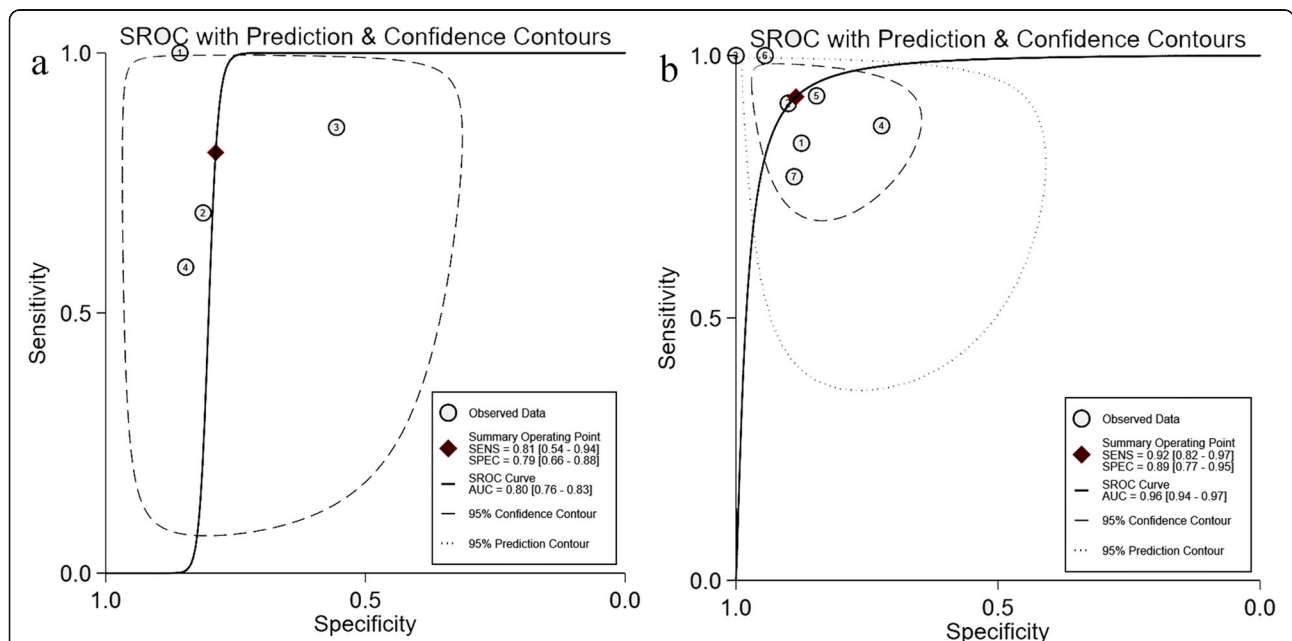
**Table 4** Diagnostic accuracy of  $\Delta V_{Peak}$  in the group of ages

Ages (mean)	Numbers	Sensitivity	Specificity	Diagnostic odds ratio	SROC (95%CI)
All patients	11	0.89 (0.77–0.95)	0.85 (0.77–0.91)	48 (15–155)	0.91 (0.88–0.93)
< 25 months	4	0.81 (0.54–0.94)	0.79 (0.66–0.88)	16 (4–64)	0.80 (0.76–0.83)
≥ 25 months	7	0.92 (0.82–0.97)	0.89 (0.77–0.95)	91 (21–385)	0.96 (0.94–0.97)

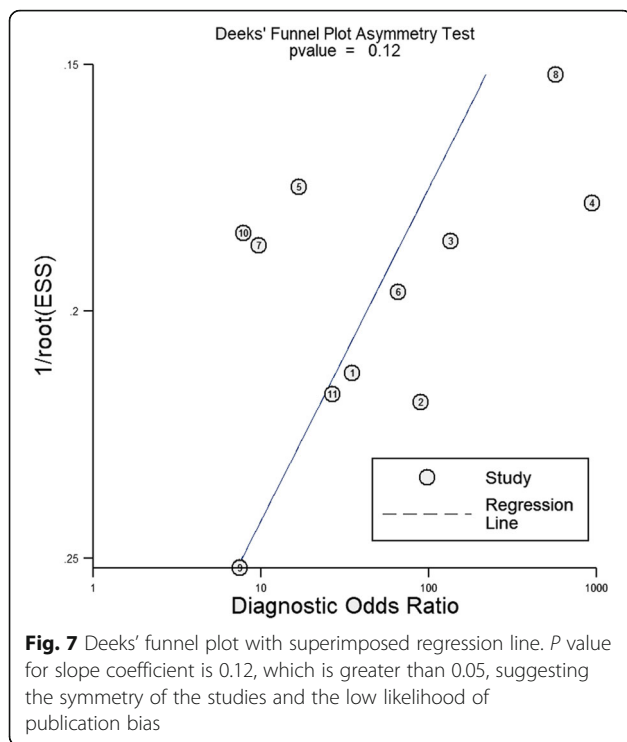
years, and comparing with demonstrating  $\Delta V_{Peak}$  is capable for predicting fluid responsiveness of ventilated children, acquiring optimal  $\Delta V_{Peak}$  threshold value of prediction possesses more clinical value. In a similar meta-analysis of respiratory variation in inferior vena cava diameter ( $\Delta IVC$ ), Si et al. [42] directly calculated the mean cutoff value of  $\Delta IVC$  with only six studies in subgroups as the optimal threshold value of  $\Delta IVC$ . In our scatter plot of  $\Delta V_{Peak}$  cutoff value, we observed that the cutoff value of  $\Delta V_{Peak}$  distributed symmetrically around the value of 12 to 13% [43]. And excluding several extreme studies, most data were centered between 12 and 13%. Combining mean and medium values, we estimated the most accurate value of  $\Delta V_{Peak}$  for prediction of fluid responsiveness in ventilated children is between 12 and 13%.

The extreme  $\Delta V_{Peak}$  cutoff values in our systematic review were 7% and 20%. Renner [32] performed volume expansion and  $\Delta V_{Peak}$  measurement after induction of anesthesia and before surgery. Without any fluid loss and hemodynamic alteration induced by surgery, such as trauma [44] and incision evaporation, patients possessed

a stable volume state, and we observed a smaller value of  $\Delta V_{Peak}$  in Renner’s study than in other included studies, with 10.1% and 5.2% separately in responsive and non-responsive group before fluid loading, which could be the reason for only 7% cutoff value of  $\Delta V_{Peak}$ . Besides, fluid time is defined as the time of fast volume expansion with colloid 400–600 ml or crystalloid 300–1000 ml, usually within 30 min [45], while Renner’s study did not clarify fluid time of volume expansion. Recent evidence indicated that fluid responsive proportion decreased as fluid time extended [14], which could be a mixed factor for the cutoff value of  $\Delta V_{Peak}$  in Renner’s study. In another extreme condition, Choi et al. [31] got a 20% cutoff value for  $\Delta V_{Peak}$ . Compared to other included studies, Choi chose 1 h after arriving at ICU as measurement time point in cardiac surgery children. However, not only blood loss caused absolute inadequate volume state, trauma and stress could also rise plant nerve disorder, leading to relative hypovolemia [46, 47]. What is more, 1-h treatment in ICU may also increase variations in the hemodynamic state. Evidence shows that postoperative hemorrhage



**Fig. 6** Summary receiver operating characteristics curve of respiratory variation of aortic peak velocity for the prediction of fluid responsiveness in **a** mean age of ventilated children < 25 months and **b** mean age of ventilated children ≥ 25 months. Circles represent each study included in the meta-analysis. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristics



is a frequent complication after cardiac surgery [48], and patients after cardiac surgery represent a challenging high-risk population with specific requirements in catecholamine and fluid therapy in face of compromised cardiac performance and pronounced systemic inflammatory response after cardiopulmonary bypass [49]. Considering reasons above, patients were in high degree hypovolemia state before volume expansion, and we indeed observed a larger value of  $\Delta V_{Peak}$  in both groups, which could finally rise for large cutoff value of  $\Delta V_{Peak}$ .

In a subgroup analysis, compared to total data analysis, the prediction accuracy of  $\Delta V_{Peak}$  decreased in the younger age group (mean age < 25 months) and increased in the older age group (mean age > 25 months), indicating that clinicians should be cautious to apply  $\Delta V_{Peak}$  in younger children, especially children under 25 months, which was not mentioned in the previous study. Compared to Desgranges et al. [23], studies that gave a lower area under the curve of ROC (less than 0.8) emerged only in new studies published in recent years, and we have reasons to believe age is a potential factor to predictive accuracy of  $\Delta V_{Peak}$ . We consider inaccurate prediction of  $\Delta V_{Peak}$  could be relative to anatomical variation in younger children due to distinctive development, especially in children with congenital heart defects [50]. Studies reported that cardiac function in the immature left ventricle might be characterized by a higher

basal contractile state, reduced compliance, and greater sensitivity to changes in afterload [51–53]. Moreover, Wolf et al. [53] found the neonatal myocardium is less responsive to preload and is vulnerable to overfilling. Due to limited data in different months phase, we failed to conclude the exact age group that optimally suitable for  $\Delta V_{Peak}$ . But children more than 3 years old could be more reliable on clinical work because of mature organs of the heart and vessels. With respect to the measurement tool of  $\Delta V_{Peak}$ , we are interested to find all younger group studies included in our research measured  $\Delta V_{Peak}$  by transthoracic or transoesophageal echocardiography. So far, no direct evidences have shown the distinction between transthoracic and transoesophageal echocardiography or the two methods could substitute for each other, but the closer measurement position to cardiac ejection, the more accurate to reflect central perfusion [41], and the two measurement methods both take close position to cardiac ejection. We concluded transoesophageal echocardiography had similar or slightly higher accuracy. Vasoactive drugs could activate  $\alpha$  and  $\beta$  receptors in the heart and vessels, augment heart rate, and increase cardiac afterload, which could influence volume state and velocity of cardiac ejection. However, Sakai et al. [54] examined the effects of adrenaline administration on changes in circulatory dynamics and cardiac function in rats pretreated with chlorpromazine, and consequently found SV did not change significantly, and SVV significantly reduced at 1 and 2 min after treatment with adrenaline, but returned back to baseline thereafter. In our study, seven included studies used vasoactive drugs, and the vasoactive group yielded an area under SROC of 0.92, which was similar to total data, indicating vasoactive drugs had no significant impact on  $\Delta V_{Peak}$ .

In our study, overall data Cochran's *Q* and  $I^2$  statistical analysis shown no significant heterogeneity, but significant heterogeneity for sensitivity existed and we still cannot rule out any potential heterogeneity. The threshold effect is one of the main causes of heterogeneity in diagnostic tests due to different cutoff values used in different studies to determine a positive (or negative) result. The Spearman correlation coefficient value in our study was 1, which meant the heterogeneity could be fully explained by the threshold effect [55, 56], which has not been explained in Desgranges' study [23].

There are some limitations in our study. Firstly, sample size and study numbers in our meta-analysis were limited, although they were twice the number than previous studies. We included 11 diagnostic tests distributed between 2008 and 2018, with only 302 sample sizes, which were much smaller than the similar scale meta-analysis [42]. We attributed this phenomenon to the fact that ventilated children requiring  $\Delta V_{Peak}$

measurement were most critical or severe trauma, such as cardiac surgery, neurosurgery, or complicated diseases hospitalized in ICU. This population was rather small and each clinical study included in our meta-analysis collected limited samples. However, even under this condition, a meta-analysis still provided valuable information on the diagnostic accuracy until proven by larger or better-conducted studies [57]. Secondly, time of volume expansion was different or not clarified in our included studies. In the recent years, Toscani and colleagues [14] conducted a large sample meta-analysis finding that responsive proportion of population had no significant correlation with the type and volume of fluid but decreased with long infusion time, especially more than 30 min. Although most included studies in our meta-analysis restricted infusion time less than 20 min, we still could not exclude infusion time as a factor for  $\Delta V_{\text{Peak}}$  accuracy. Thirdly, except Favia et al. [38] using the peripheral artery wave contour analysis technique, the gold standard index was measured by transthoracic or transoesophageal echocardiography. To our knowledge, the closer measurement position to cardiac ejection, the more accurate prediction for hemodynamic indices to reflect central perfusion [41]. However, we failed to find difference after excluding Favia's study (see Additional file 2), but we still could not rule out reference index measurement as a potential factor that influence accuracy of  $\Delta V_{\text{Peak}}$ , and more studies in the future could bring different results. Fourthly, included studies picked different time to start fluid challenge and  $\Delta V_{\text{Peak}}$  measurement, such as after anesthesia, during surgery, sternum closure, or even arriving at ICU. However, complicated operating procedure could rise variable hemodynamic state in different measurement points, which could not be neglected to our meta-analysis. Lastly, in subgroup analysis, we found age was a factor that influenced  $\Delta V_{\text{Peak}}$  accuracy. However, due to included studies providing a mean value of age rather than a limited scale of age, we only found a decline tendency of prediction accuracy of  $\Delta V_{\text{Peak}}$  rather than giving an accurate value of age that  $\Delta V_{\text{Peak}}$  should be recommended applied in. Therefore, more new studies are needed to be done in the future.

## Conclusions

Overall,  $\Delta V_{\text{Peak}}$  has a good ability in predicting fluid responsiveness of children receiving mechanical ventilation and the optimal threshold value of  $\Delta V_{\text{Peak}}$  to predict fluid responsiveness is reliable between 12 and 13%. However, we observed that this ability decreased in younger children, especially mean age less than 25 months; thus, we expect more studies to make a statistic treatment in the future.

## Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13054-019-2647-7>.

**Additional file 1.** Subgroup analysis of the gold standard index, vasoactive drugs and fluid types. **Table S1.** Subgroup analysis of the gold standard index, vasoactive drugs and type of drugs. **Figure S1.** Summary receiver operating characteristics curve of respiratory variation of aortic peak velocity for the prediction of fluid responsiveness in subgroups of gold standard index, fluid types and vasoactive drugs.

**Additional file 2.** Excluded one retrospective study's meta-analysis. **Figure S2.** Summary receiver operating characteristics curve of respiratory variations of aortic peak velocity for predicting fluid responsiveness in the left 10 studies (excluding Favia's study [38]).

## Abbreviations

$\Delta V_{\text{Peak}}$ : Respiratory variation of aortic peak velocity; AUSROC: Area under the summary receiver operating characteristic curve; BP: Blood pressure; CI: Cardiac index; CO: Cardiac output; CVP: Central venous pressure; DOR: Diagnostic odds ratio; PAWP: Pulmonary artery wedge pressure; PPV: Pulse pressure variation; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; SROC: Summary receiver operating characteristic curve; SV: Stroke volume; SVI: Stroke volume index; SVV: Stroke volume variation

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## Authors' contributions

JG and XW designed the study and modified the manuscript. XW, LJ, and SL participated in the design of the study, performed the statistical analysis, and drafted the manuscript. Search strategy, study selection, data extraction, and quality assessment were performed independently by XW and LJ. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Not applicable

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no competing interests.

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