Original article

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Left ventricular end-diastolic volume index as a predictor of fluid responsiveness in children with shock

Ahmad Bayu Alfarizi, Antonius Hocky Pudjiadi, Rismala Dewi

Abstract

***Objective*: To identify the role of left ventricular end-diastolic volume index as a predictor of fluid responsiveness in children.**

***Design*: This was a diagnostic study in children with shock in the Emergency Room and Pediatric Intensive Care Unit of Cipto Mangunkusumo Hospital from June to November 2018. The left ventricular end-diastolic volume index measurements were performed using ultrasonic cardiac output monitor and compared to the increase in stroke volume of ≥15% after fluid challenge as fluid responsiveness criteria. Samples were categorized into fluid responsive and non-responsive.**

***Results*: Out of 40 subjects, 60 fluid challenge samples were obtained. There were 31 and 29 samples in the fluid responsive and non-responsive group, respectively. There was no significant difference in mean left ventricular end-diastolic volume index between the two groups (p=0.161). The area under the receiver operating characteristic (AUROC) of the left ventricular end-diastolic volume index was 40.9% with a cutoff value of 68.95 ml/m^2. The sensitivity and specificity were 45.16% and 44.83%, respectively. At the left ventricular end-diastolic volume index value of 81.10 ml/m^2, the specificity was 72.41% with 22.6% sensitivity.**

***Conclusion*: This study cannot justify the use of left ventricular end-diastolic volume index can act as a predictor of fluid responsiveness in children.**

Key words: Fluid responsiveness, left ventricular end-diastolic volume index, shock, hemodynamics.

Introduction

Pediatric shock is a leading problem in both emergency and intensive pediatric care. In tertiary care centers of developed countries such as the USA, shock is reported to occur in 37% of the patients. (1) Children presenting with circulatory failure show a higher mortality rate compared to those without (11.4% as compared to 2.6%). (2) Yuniar (3) reported that 38.1% of cases with circulatory failure in Cipto Mangunkusumo National General Hospital was of hypovolemic shock.

Fluid resuscitation remains one of the primary tools in managing circulatory failure in children. In cases with clearly defined etiology related to massive fluid loss, such as hypovolemic shock due to hemorrhage or diarrhea, fluid resuscitation is the principal therapy of choice. However, in cases without any clear evidence of fluid loss, fluid resuscitation needs to be carefully considered. In patients whose fluid resuscitation is not required, incorrect administration may result in morbidity and mortality. (4,5)

A physician needs to consider whether a patient will receive an actual benefit from the act of fluid resuscitation. This can be determined by evaluating whether a patient falls into groups of fluid responders or fluid non-responders. Fluid responsiveness is defined as an increase of ≥15% in stroke volume and/or cardiac index in response to a fluid challenge. (5-7)

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Evaluating the status of intravascular volume is hardly a simple task. The applications of clinical parameters are often inaccurate, with only up to 50% accuracy rate even when done by an expert. (5) In patients with hemodynamic imbalance, only 50% falls into the group of fluid responders. (7-9)
There are several methods available to assess fluid responsiveness: static indices, dynamic indices, and fluid challenge. Some of those methods come with limitations such as their invasive nature and high cost, while others require certain conditions that keep them from being able to be used for all patients. (5,9,10)
Left ventricular end-diastolic volume (LVEDV) is a hemodynamic parameter commonly used to represent cardiac preload. The Frank-Starling law uses LVEDV and stroke volume to demonstrate the relationship between preload and systolic function. The measurements of left ventricular end-diastolic volume index (LVEDVI) in order to determine preload have been performed using echocardiography, which requires a certain level of expertise. (5,6) Studies have reported that LVEDVI has a low correlation with fluid responsiveness, but most of these studies were done in adult population with notable anatomic and physiologic differences with children. (4) This study aimed to determine the role of LVEDVI as a predictor of fluid responsiveness towards fluid resuscitation in children with shock.

Patients and methods

This study was a diagnostic, cross-sectional study done in children with shock. This study took place from June 2018 to November 2018. All patients ranging from 1-month to 18-year old with shock admitted to the Pediatric Intensive Care Unit of Cipto Mangunkusumo National General Hospital who received fluid challenge were included. The inclusion criteria were children with shock whose parents have signed the informed consent. The exclusion criteria were children with anatomical disorders of the heart, congestive heart failure, lung edema, or multiple congenital disorders. Forty samples were collected through consecutive sampling, among those patients, 60 fluid challenges were performed and analyzed. The index test of this study was the LVEDVI, with the fluid challenge technique as the reference test.
Measurements of hemodynamic parameters were done in all patients using ultrasound cardiac output monitor (USCOM) before and after fluid challenge. Measurements were performed by a single operator. LVEDVI was calculated with Inotropy 7.2 software using the Smith-Madigan formula. Samples were placed into groups of LVEDVI above or the same as the cutoff point, and LVEDVI below the cutoff point based on the receiver operating characteristic (ROC) curve. LVEDVI measurements were performed three times and presented as an average value. In patients who received fluid loading, the fluid challenge was done twice; after the first fluid challenge, the patient was given another fluid resuscitation of 10 ml/kg, with measurements of LVEDVI and stroke volume done as before. In cases of hypovolemic shock, measurements of LVEDVI did not delay the act of fluid resuscitation. Samples were also grouped based on their fluid responsiveness; patients were defined as fluid responsive if ≥15% increase in stroke volume was observed after fluid challenge.
Patients with shock included those found with (a) tachycardia; (b) perfusion disturbances, with 3 out of the following present: central pulse quality higher than the peripheral pulse quality, cold extremity, pale or mottled skin, capillary refill time (CRT) >2 seconds, pulse pressure narrowing <20 mmHg, diuresis <1 ml/kg/hour for weight <30 kg or <0.5 ml/kg/hour for weight ≥30 kg, loss of consciousness or decline in mental status; or (c) decrease in systolic pressure (below 5th percentile based on the chart relative to age, height, and sex).
The collected data were presented as narration, tables, and graphs. Normality tests were conducted for the numerical data using the Kolmogorov-Smirnov test. We performed the T-test for normally distributed data and the Mann-Whitney U test for otherwise. The LVEDVI before fluid challenge was projected as the predictor of fluid responsiveness to the ROC curve to find the optimal cutoff point as well as define the sensitivity and specificity. This study was approved by the Ethical Committee of Medical Research, Faculty of Medicine, Universitas Indonesia.

Results

Of 1488 patients admitted to the Intensive Care Unit, we found 40 patients who qualified for the study and 60 fluid challenges were done. The profile of study subjects is presented in **Table 1**.
Of 60 fluid challenges, we found 31 fluid responsive cases and 29 fluid non-responsive cases based on evaluating the presence of ≥15% stroke volume increase. Therefore, the prevalence of fluid responsive cases was 51.67%. **Table 2** shows the hemodynamic parameters before fluid challenge between the fluid responsive group and fluid non-responsive group. The parameters, which show a statistically significant mean differences between

the two groups were stroke volume index (SVI) and cardiac index (CI) ($p<0.05$), while LVEDVI did not show a significant difference.

In this study, the evaluation of LVEDV and LVEDVI were performed before and after fluid challenge. The measurements before fluid challenge was evaluated as the predictor of fluid responsiveness. By using the ROC method, the area under the curve (AUC) value of 55.4% was obtained for LVEDV (CI 95%, 40.5%-70.2%) with p=0.473, and AUC value of 40.9% for LVEDVI (CI 95%, 26.5%-55.40%) with p=0.228 (**Figure 1**). The curve demonstrating the optimal cutoff point of LVEDVI before fluid challenge is shown in **Figure 2**. The optimal cutoff point of the curve is shown by the diagonal cutoff point between sensitivity and specificity, which is the LVEDVI value of 68.95 ml/m^2. The sensitivity and specificity of this value were 45.16% and 44.83%, respectively. The complete result of the diagnostic testing of LVEDVI as a predictor of fluid responsiveness can be seen in **Table 3**.

- Sensitivity 45.16% (CI 95%, 27.32-63.97%).
- Specificity 44.83% (CI 95%, 26.45-64.31%).
- Positive likelihood ratio 0.82 (CI 95%, 0.49-1.36).
- Negative likelihood ratio 1.22 (CI 95%, 0.73-2.05).
- Prevalence 51.67% (CI 95%, 38.39-64.77%).
- Positive predictive value 46.67% (CI 95%, 34.49-59.25%).
- Negative predictive value 43.33% (CI 95%, 31.36-56.13%).
- Accuracy 45% (CI 95%, 32.12-58.39%).

Figure 2 also illustrates that higher LVEDVI is followed by higher specificity but lower sensitivity. LVEDVI value of 56.25 ml/m^2 has a sensitivity of 80.6% with 10.3% specificity, while the LVEDVI value of 50.25 ml/m^2 has 90.3% sensitivity and 6.9% specificity. At the LVEDVI value of 81.10 ml/m^2, the specificity is 72.41% with 22.6% sensitivity. LVEDVI value of 97.85 ml/m^2 has 82.76% specificity with 3.2% sensitivity. As a guideline, LVEDVI can be used as a predictor of fluid responsiveness at a moderately high specificity (**Table 4**).

Discussion

Body fluid status assessment plays an important role in diagnosing and managing homeostatic disturbances of body fluid in intensive and emergency care settings. Only about 50% of patients with signs of circulatory failure respond to fluid resuscitation. (4,10-12) Fluid overload may lead to elevated morbidity and mortality in patients. (8) There are several methods to evaluate a patient's fluid volume status, but each of these methods comes with their own limitations. The ideal method to be used should be easy to perform, non-invasive, and reliable.

In this study, we found 31 fluid responsive cases and 29 fluid non-responsive cases after fluid challenge based on ≥15% increase in stroke volume. Therefore, the prevalence of fluid-responsive subjects in this study was 51.67%. This finding was in line with the study performed by Mckenzie and Noble (13) as well as the study by de la Oliva, et al, (14) which reported that fluid bolus only increases cardiac output in 50% of patients with shock. Excessive fluid resuscitation may result in a positive fluid balance and pulmonary edema, which are associated with higher morbidity and mortality. (4,14-16)

Clinical evaluation cannot be used to predict fluid responsiveness. On the other hand, despite some studies have shown that dynamic indices can be highly predictive towards fluid responsiveness, its usage is limited for patients with controlled positive pressure ventilation, and it fails to predict fluid responsiveness in patients with spontaneous respiration, low tidal volume, low pulmonary compliance, high-frequency oscillation ventilation or respiratory rate over 40 times per minute, arrhythmia, and elevated intra-abdominal pressure. (10,14)

When performing a study about a new diagnostic tool, a valid and reliable standard criterion to evaluate the diagnostic tool is essential. In this study, we evaluated the application of LVEDVI as a predictor of fluid responsiveness.

Static parameters such as pressure or volume are parameters that are originally used to determine response to fluid responsiveness before the development of dynamic parameters. Several studies performed on adults have shown that static indices can be used to evaluate preload status, but none were associated with fluid responsiveness. (13,17) Static parameters may be used to show the point location on the Starling curve, but not its movements at the steep part of the curve. (13) This explains why static parameters cannot be used as a predictor of fluid responsiveness. There were only a few studies that reported LVEDVI as a predictor of fluid responsiveness; therefore, we also refer to studies that involve other static parameters such as left ventricular end-diastolic area index (LVEDAI), right ventricular end-diastolic volume (RVEDV), and pulmonary artery occlusion pressure (PAOP).

In this study, the difference between LVEDV and

LVEDVI between the groups of fluid responsive cases and fluid non-responsive cases were not significant. This supports the study by Reuter, et al (18) which reported no significant difference between LVEDAI before and after fluid bolus (r=-0.45; p>0.05). Michard, et al (19) also reported no significant difference in left ventricular end-diastolic area (LVEDA) after fluid resuscitation with the percentage of cardiac output increase (r^2=0.11; p=0.17).

By using the ROC method, we found the AUC of 55.4% (p=0.473) for LVEDV and 40.9% (p=0.228) for LVEDVI. The interpretation of AUC was done using two approaches, which were the statistical approach and clinical approach. Statistically, the AUC of 50-60% is very weak. The other approach to interpret the AUC value is the clinical approach, which may or may not support the statistical approach. Statistical interpretation is only done when there is a complete lack of logical ground for a clinical interpretation.

The AUC of 40.9% (p=0.228) for LVEDVI did not show a significant difference with 50% AUC. This was in line with the report by Tavernier, et al (20) of a study, which compared various hemodynamic parameters and concluded that LVEDA has a lower area under the receiver operating characteristics (AUROC) compared to systolic pressure variation (0.77 CI 95%, 0.59-0.92 compared to 0.94 CI 95%, 0.8-0.99). A different result was reported by de la Olivia, who concluded that the global end-diastolic volume index (GEDVI) can be used as a predictor of fluid responsiveness with the AUC of 75% (p<0.001). (14) The study was performed on 75 patients by using PiCCO for hemodynamic monitoring.

The optimal cutoff point of LVEDVI before fluid challenge was ≥68.95 ml, with the sensitivity and specificity of 45.16% and 44.83%, respectively. Statistically, this value shows that LVEDVI is a weak parameter for predicting fluid responsiveness. From the clinical standpoint, the specificity can be ignored in order to increase the sensitivity. A high sensitivity fits the goal of screening, which is to include as many fluid responsive patients as possible and decreasing the number of false negatives. The LVEDVI of 56.25 ml/m^2 had 80.6% sensitivity with a specificity of 10.3%. The LVEDVI of 50.25 ml/m^2 had 90.3% sensitivity and 6.9% specificity. The positive predictive value and negative predictive value of LVEDVI for fluid responsiveness were reportedly low, at 46.67% and 43.33%, respectively.

From the other aspect of clinical importance, LVEDVI can also be used on the last stage of the diagnosis, in which the cutoff point with high specificity will be the better choice in order to reduce the number of false positives. In this study, LVEDVI at the cutoff point of 81.10 ml/m^2 had 72.41% specificity with 22.6% sensitivity, while LVEDVI of 97.85 ml/m^2 had 82.76% specificity with 3.2% sensitivity. This study is in line with another study that used the GEDVI parameter, in which higher GEDVI correlated with higher stroke volume and cardiac output. (21)

Relationship with previous studies

This study was unable to prove that LVEDVI can be used as a predictor of fluid responsiveness. This is in accordance with studies performed in the adult population, which concluded that static parameters cannot be used to predict fluid responsiveness.

A study done by Wiesnack, et al (15) reported that the increase in right ventricular end-diastolic volume index (RVEDVI) is significantly correlated to increase in stroke volume after fluid resuscitation (r^2=0.55; p=0.001), but it does not serve as a good predictor of fluid responsiveness. LVEDAI was the only hemodynamic parameter in the study, which was reported to be correlated with fluid responsiveness, albeit with a low correlation (r^2=0.38; p<0.01). (15)

In 2013, Gan, et al (22) performed a systematic review regarding fluid responsiveness in children. This systematic review was done because of the lack of studies about this topic in the pediatric population. Twelve publications from 1947-2013 were collected and 24 variables were analyzed. The study reported that only respiratory variation in aortic blood flow peak velocity, which is a dynamic parameter, could be used as a predictor of fluid responsiveness, while none of the static parameters were shown to be able to predict fluid responsiveness. LVEDVI was not one of the parameters present in the studies analyzed in this systematic review.

Nahouraii and Rowell (23) in their article about the application of static parameters to measure preload and assessing fluid responsiveness concluded that despite several studies summarizing that there is a relationship between volumetric static parameters and fluid responsiveness, this relationship had a weak correlation. One of the possible explanations for this is that static parameters are very dependent on ventricular compliance and contractility, which are found to be compromised in most critically ill patients. (10,24,25) Static parameters do not operate on a linear scale as illustrated by the Frank-Starling law. The Frank-Starling law, at its core,

simply explains the intrinsic nature of the myocardium. The increase in length of the cardiac muscles during ventricular filling is positively correlated with the increase of ventricular pressure and the Frank-Starling curve shows that LVEDV has a linear relationship with stroke volume.

This concept stems from an in vitro experiment performed on an isolated heart outside the organism's body, which in reality is actually influenced by a lot of factors. In 1954, Sarnoff and Berglund reviewed the Frank-Starling law in a dog with a complete circulation system. When the dog's coronary artery was restricted, the left ventricular function and maximum stroke volume became lower, and despite further increases in preload, the left ventricular function and stroke volume decreased. The study showed that left ventricular function and stroke volume rise following an increase in preload up to the point where the curve reaches a plateau, demonstrating the curvilinear relationship between left ventricular function and stroke volume. This finding showed that stroke volume and LVEDV are influenced by a lot of complex and dynamic physiological factors such as the nervous system, metabolic function, neurohormonal activation, interaction between the heart and the lung, oxygen supply, and consumption by the tissues, contractility, and afterload. (26-28)

Guerin, et al also elaborated a similar explanation about this phenomenon. The first one was that there was no marker of preload, which represented an actual measure of preload, while another was that there were multiple curves that represented the relationship between stroke volume and ventricular preload on the Frank-Starling curve, which depended on the ventricular contractility. Guerin, et al further explained that despite static parameters being unable to predict fluid responsiveness, they could still be used as safety parameters during fluid administration.

A study by Endo, et al (11) reported that patients with cardiac dysfunction due to sepsis marked by left ventricular ejection fraction (LVEF) <50% did not have higher GEDVI values than patients without cardiac dysfunction. This study also found no relationship between GEDVI and stroke volume variation (SVV) in groups with and without myocardial dysfunction, showing that there were other factors influencing static parameters other than contractility.

Another possible reason which may explain why LVEDV is not a good predictor of fluid responsiveness is that this parameter is measured using a technique that is not completely appropriate for measuring LVEDV. LVEDV measurement using echocardiography has been reported as having technical limitations due to it being a two-dimensional measurement. (29,30) Three-dimensional volumetric measurement can be done using transesophageal echocardiography (TEE) which can reflect the LVEDV value more accurately, but only a few studies used TEE due to the need for technical expertise. (31)

Implications

Our findings imply that the literature and studies that we found offered inconclusive explanations and inconsistent results in elaborating the definitive cause of why static parameters are unreliable in measuring preload and predicting fluid responsiveness. In this study, LVEDVI was the result of a mathematical calculation from the value of stroke volume and other variables, and whether the factor of computational calculation was able to completely reflected the hemodynamic physiologic response required a further explanation, which could not be inferred from this study alone.

Strengths and weaknesses

The strength of this study was that this was the first study in children using the LVEDV parameter as a predictor of fluid responsiveness measured using USCOM. The limitation of our study was the heterogeneity of our subjects in terms of age groups and diagnosis, both of which might influence the results of the study. This study was also unable to determine whether the patient was currently in the preload-dependent phase or preload independent phase of the Frank-Starling curve.

Conclusion

This study cannot prove LVEDVI can act as a predictor of fluid responsiveness. There was no significant difference in mean LVEDVI before fluid challenge between the fluid responsive group and fluid non-responsive group. The optimal cutoff point of LVEDVI before fluid challenge was 68.95 mL with very low accuracy (40.9% AUC) as well as low sensitivity and specificity. Clinically, the LVEDVI parameter may be considered as a predictor of fluid responsiveness at the cutoff point of $\geq$81.10 ml/m^2 with >72.41% specificity or for screening at the cutoff point of $\geq$50.25 ml/m^2 with >90% sensitivity.

Conflict of interest and funding

There is no conflict of interest to declare by all authors in this study. This study didn't receive any external funding.

Table 1. Profile of study subjects

Characteristic	n=40
Sex, n (%)	
Male	22 (55)
Female	18 (45)
Age (month), n (%)	
1-11	3 (7.5)
12-24	12 (30)
25-60	6 (15)
61-144	9 (22.5)
>144	10 (25)
Nutritional status, n (%)	
Severely underweight	3 (7.5)
Underweight	12 (30)
Normoweight	19 (47.5)
Overweight	2 (5)
Obesity	4 (10)
Type of shock, n (%)	
Hypovolemic shock	17 (42.5)
Cardiogenic shock	2 (5)
Distributive shock	8 (20)
Obstructive shock	4 (10)
Septic shock	9 (22.5)

Table 2. Characteristics of hemodynamic parameters before fluid challenge between the fluid responsive group and fluid non-responsive group

Parameter	Fluid responsive (n=31)	Fluid non-responsive (n=29)	p
Heart rate (beat/min), median (range)	137 (57-192)	153 (50-184)	0.188**
MAP (mmHg), mean (SD)	69.5 (13.40)	75.5 (14.19)	0.099*
SV (ml), median (range)	34 (9.7-99)	18 (11-82)	0.454**
SVI (ml/m^2), median (range)	28 (17-59)	35 (17-67)	0.030**
CO (l/min), median (range)	3.2 (0.84-7.80)	2.7 (0.91-9)	0.941**
CI (l/min/m^2), median (reange)	3.9 (0.96-8.50)	4.8 (1.80-12)	0.032**
LVEDV (ml), median (range)	50 (8.4-244)	40 (23.3-240)	0.473**
LVEDVI (ml/m^2), mean (SD)	69.1 (15.19)	75.2 (18.31)	0.161*

Legend: MAP=mean arterial pressure; SV=stroke volume; SVI=stroke volume index; CO=cardiac output; CI=cardiac index; LVEDV=left ventricular end-diastolic volume; LVEDVI=left ventricular end-diastolic volume index.
* T-Test
** Mann-Whitney U Test

Table 3. Diagnostic testing of LVEDVI before fluid challenge

Variable		Fluid responsiveness		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
		Yes	No				
LVEDVI (ml/m^2)	≥68.95	14	16	45.16	44.83	46.67	43.33
	<68.95	17	13				

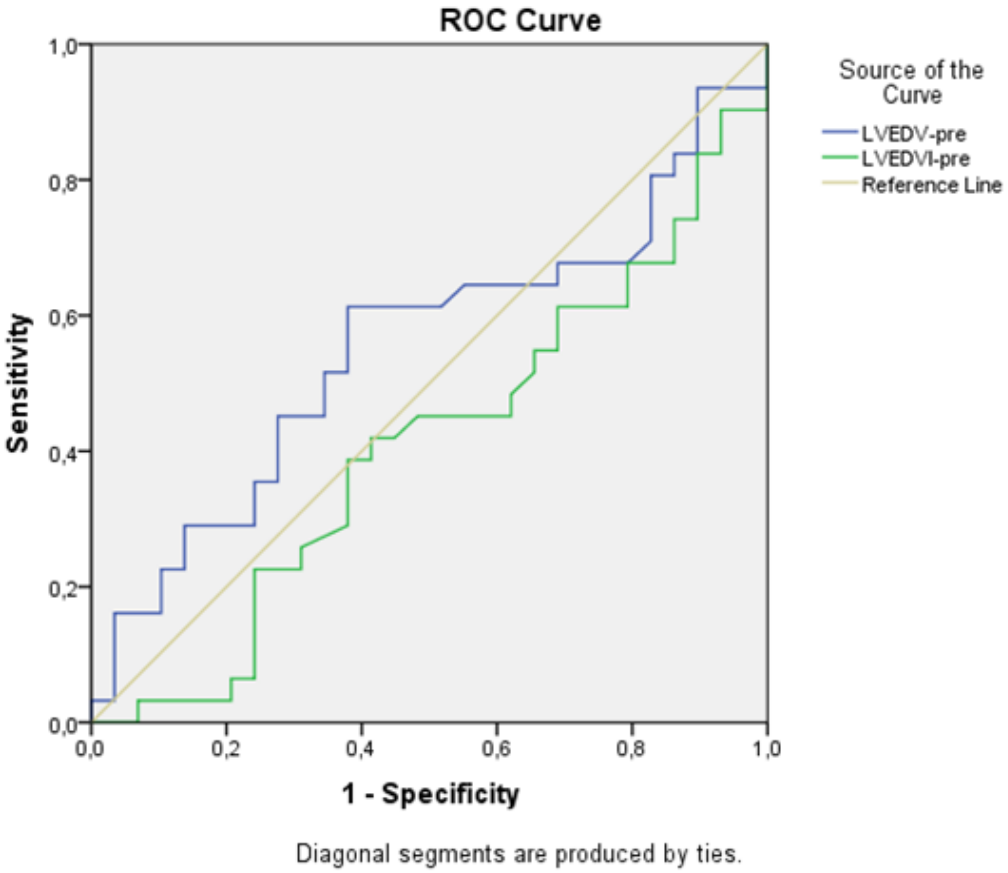
Legend: LVEDVI=left ventricular end-diastolic volume index.

Table 4. LVEDVI as a predictor of fluid responsiveness

LVEDVI (ml/m^2)	Specificity (%)
≥80	≥70
70-80	55-70
<70	<55

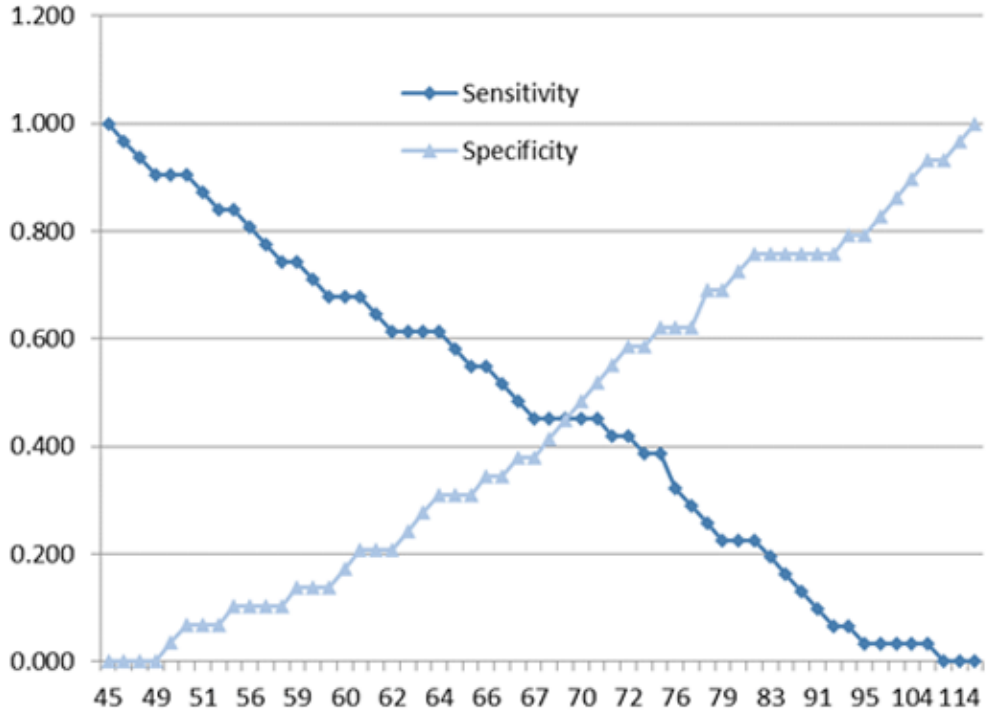
Legend: LVEDVI=left ventricular end-diastolic volume index.

Figure 1. ROC curve of LVEDV and LVEDVI before fluid challenge



Legend: ROC=receiver operating characteristic; LVEDV=left ventricular end-diastolic volume; LVEDVI=left ventricular end-diastolic volume index.

Figure 2. LVEDVI cutoff point curve before fluid challenge



Legend: LVEDVI=left ventricular end-diastolic volume index.

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