Prediction of fetal outcome without intrauterine intervention using a cardiovascular profile score: a systematic review and meta-analysis

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Abstract

Objective: With the help of fetal echocardiography, cardiovascular profile score (CVPS) can be evaluated. However, no general agreement has been recognized on the prediction value of CVPS on fetal adverse outcome.

Methods: Literature review has identified up to Nov 2012 in the databases. Meta-analysis was performed in a fixed/random-effect model using Revman 5.1.1 and Meta-disc 1.4. The differences among different cut-offs were measured by STATA 11.0.

Results: Result from seven studies reported an outcome in favor of significant lower CVPS in fetus of adverse outcome with std. mean difference of $1.17$ (95% CI $1.78$, $0.55$). The overall performance of CVPS prediction adverse outcome evaluated as area under the summary receiver operating characteristic curves (AUC) was 0.8777. The AUC of CVPS was 0.8728 and the AUC of CVPS was 0.7207. However, the result indicated the performance of CVPS prediction adverse outcome had a statistical significance comparing to other two cut-offs.

Conclusion: Analysis has proven the CVPS is a credible index for predicting fetal adverse outcome. And once CVPS decreased at eight, the patient should be observed carefully. With the CVPS dropped at seven, treatment is demanded immediately while some cases suffer irreversible cardiac dysfunction.

Keywords

CVPS, echocardiography, fetal diagnosis, meta-analysis, prognosis

Introduction

Fetal heart dysfunction and fetal hydrops are associated with significant mortality and morbidity [1,2]. In clinical practice, redistribution of fetal cardiac output, altered diastolic and systolic function, tricuspid regurgitation, abnormal systemic venous blood velocity waveforms, myocardial hypertrophy and cardiomegaly can lead to fetal heart dysfunction and fetal hydrops [3,4], which can finally result in intrauterine growth restriction (IUGR) [5,6]. With technological advance is a constant in ultrasound imaging, as each generation of machines improves on earlier models, with the aim of improving scan quality. So it is available for us to estimate the heart structures and function during pregnancy. During fetal heart rate monitoring, the biophysical profile score, umbilical artery velocimetry, cardiovascular profile score (CVPS) and tei-index are used widely in predicting outcomes of fetuses with cardiac dysfunction and for determining the time for delivery of hydrops fetuses [3,7,8]. Abnormalities in fetal cardiovascular hemodynamics have been shown to precede abnormalities in fetal heart tracings. And the fetal ultrasound has been proved a reliable diagnostic tool in fetal life [9].

CVPS is a concept similar to the biophysical profile score of Manning et al. [10]. It comprises five categories of ultrasound marker in a 10-point scoring system that combines variables known to be associated with perinatal mortality: hydrops, cardiomegaly, abnormal myocardial function, redistribution of cardiac output and abnormal venous Doppler. CVPS reflects the overall status of fetal cardiac function. It has been demonstrated by multiple studies that when CVPS decreased, perinatal mortality is high. However, a specific value for clinical decision-making is still controversial, such as for continuation of pregnancy versus induction of delivery, and start of medication treatment versus observatory care [1,2,11].
Any one of these markers may become abnormal prior to the onset of hydrops fetus and all have been associated with poor fetal outcome. As mentioned above, which cut-off of CVPS has the most powerful prediction value of adverse fetal outcomes is still debated. Thus, based on meta-analysis, a pooled result has been done to confirm the differences of CVPS between adverse outcomes fetuses and common outcomes fetuses. Moreover, the accuracies of different cut-offs of CVPS in predicting adverse outcomes are drawn according to their sensitivities, specificities and diagnostic odds ratio (DOR), hoping to find out the most suitable value for fetal treatment and intervention, or for terminating pregnancy in nature disease process. The comparison of values of summary receiver operating characteristic (SROC) among three cut-offs have been done, to find how cut-offs impact CVPS prediction value. Therefore, the objective of this meta-analysis is to evaluate the prediction of fetal outcome without intrauterine intervention using CVPS.

Methods

Search strategy

We searched PubMed, Ovid Embase, the Cochrane Central Register of Controlled Trials, and World Health Organization clinical trials registry registry center using a high sensitive and high specific search strategy. The research strategy was “(cardiovascular profile score OR CVPS) AND (prenatal OR antenatal OR intrauterine OR in utero) AND (outcome OR prognosis)”. Search was updated to Nov 2012. The language restriction was used only for English published papers.

Study selection

Citations initially selected by systematic search were first retrieved as title and/or abstract and preliminarily screened. Potentially relevant reports were then retrieved as complete manuscripts and assessed for compliance to inclusion and exclusion criteria.

The inclusion criteria were as follows: (1) the patients were evaluated according to similar fetal echocardiography and ultrasound; (2) controlled study; (3) the comparison were made between fetus with adverse outcome and fetus with common outcome, otherwise, these groups data would not be included into this meta-analysis; (4) contained the date which can calculate the true positive, false positive, false negative and true negative; or the sensitivity, specificity of the specific CVPS predicting the adverse outcome and (5) follow-up lasted to neonatal period.

The exclusion criteria were as follows: (1) the total sample size was quite small; (2) the same cohort had been studied in other study; (3) unable to construct 2 × 2 table; (4) undergoing fetal intervention during pregnancy and (5) conferences articles.

Data collection and quality assessment

Two investigators (Yifei Li and Jie Fang) independently assessed eligibility of reports at the title and/or at abstract level, with a third reviewer (Kaiyu Zhou) determining the divergences together; studies that met the inclusion criteria were selected for further analysis. The quality assessment was completed by the two investigators independently according to the quality assessment guidelines of non-randomized controlled interventions study by Deeks et al. [12]. The main contents were: (1) method of group assignment (assignment made by the doctors undergoing the studies, by the patients will, combine the two methods together); (2) each group was balanced at baseline according to design of studies (subgroup had been drawn from the same research center, or the same strategy; and all the diagnosis had been made with similar echocardiography equipments); (3) described the factors could influence the prognosis (formation of included patient, including gestation age, weight, administration, Apgar score, chromosomal abnormalities and subtypes characteristics, etc.) and (4) controlled the bias of studies (including stratified sampling and subgroup analysis).

Evaluation indicators

The mean CVPS between fetus with adverse outcome and common outcome was evaluated, and the continuous varies were calculated as mean ± standard deviation (SD). The test performance of different cut-offs of CVPS for predicting fetal adverse outcome was measured by the following indicators: sensitivity, specificity and DOR. Sensitivity was represented by the proportion of fetus with heart malformation that was correctly identified by the positive results of different types of echocardiography. Specificity was represented by the non-heart malformation cases that were correctly identified by the negative results of different types of echocardiography. Moreover, it was more reliable to define the summary of test performance using DOR than simply pooling sensitivity and specificity together across the studies. DOR was an independent indicator ranging from 0 to infinity, which represented how much greater the odds of having fetal congenital heart disease were for patient with a positive detecting result than for patient with a negative ultrasound result. The higher the DOR, the better and the discriminatory ability of the test was. SROC curve was plotted based on the combination of sensitivity and specificity, and the area under the curve (AUC) value was then calculated as a global measurement of test performance. The closer the AUC was to 1, the better the test performance. And the differences of sensitivity and specificity among all groups were also determined by $X^2$ test.

Publication bias

Publication bias was tested using funnel plots by Revman 5.1.1. When the figure was symmetric, the data were no bias of publication. However, if the figure was asymmetric, the bias of publication was existed.

Heterogeneity

The $X^2$ test was used to examine heterogeneity in pooling sensitivity and specificity. The Cochran-$Q$ test was used to examine heterogeneity in pooling DOR. Heterogeneity was considered to be statistically significant when $p < 0.05$ in these qualitative tests. We also conducted the $I^2$ test in every pooling analysis to quantitatively estimate the proportion of total variation across studies that was attributable to
heterogeneity rather than chance. The $I^2$ value would range from 0 to 100%, with a value over 50% indicating significant heterogeneity. The existence of a threshold effect would manifest as a curvilinear shape in the SROC curves.

**Sensitivity analysis**

To determine whether any single study was incurring undue weight in the analysis, we systematically removed one set of study data and checked the pooled results for the remaining studies to see if they changed significantly. The sensitivity analysis was conducted for every study.

**Statistical analysis**

Data were analyzed using RevMan 5.1.1 and Meta-Disc Version 1.4 [13]. And the Z test of evaluating the performance among different cut-offs of CVPS were analyzed using STATA version 11.0. Because of potential heterogeneity among studies, effect sizes were pooled by random-effects models of DerSimonian and Laird in Meta Disc [14]. Empty cells were handled using a 0.5 continuity correction.

**Results**

**Study evaluation**

A total of 81 citations were retrieved by the method aforementioned. After reading titles and abstracts, 68 citations were excluded according to the selection criteria, and identified the initially 13 articles [9,15–26]. However, none articles were added by manual retrospective research after reading related publications. Among them, six articles were excluded by reading the completed articles [17,18,20–22,25], including four articles were unable to construct 2 × 2 table [18,20–22], two articles focused on efficacy of fetal treatment using CVPS [17,25]. At last seven articles for prediction of CVPS on fetal survival were enrolled into the meta-analysis (Figure 1) [9,15,16,19,23,24,26]. Among these seven studies, six studies were about comparison of mean CVPS between adverse outcomes and common outcomes fetus, four studies evaluated the prediction value of CVPS ≤8, three studies evaluated the prediction value of CVPS ≤7 and three studies evaluated the prediction value of CVPS ≤6. The quality of all the articles were acceptable, with described the factors might influence the prediction value and the method of allocation in detail. Table 1 showed the basic characteristics of included studies and Table S1 showed the quality evaluation of these studies, all the studies were qualified for inclusion criteria.

**Publication bias**

Funnel plots were used to evaluate the publication bias of included studies. Each dot represents a study and the distance between each dot and the vertical line suggests bias in each study. The absence of any asymmetric distribution suggested no publication bias. While the asymmetric distribution existed, this indicated that publication bias existed. The funnel plots had been done for efficacy, safety and recurrent thrombus event of patent foramen ovale and atrial septal defect separated. The results showed that there was some publication bias in these evaluated studies, with an asymmetric triangle figure (Figure 2), so the results should be treated seriously.

**Mean CVPS comparison**

The comparison of mean CVPS between adverse outcomes and common outcomes was done to confirm the efficacy of CVPS. For mean CVPS comparison enrolled the 324 cases in the six studies, consisting 107 cases with adverse outcomes and 217 cases with common outcomes. The mean CVPS had significant difference between the adverse outcomes fetus and the common outcomes fetus (Std. mean difference = −1.17, 95% CI, −1.78, −0.55, $p = 0.001$). There was heterogeneity across studies ($I^2 = 75\%$), and was analyzed by random effect model (Figure 3).

**Overall prediction performance of CVPS**

**CVPS ≤6**

Overall prediction performance of CVPS ≤6 (Table 2) shows the overall performance of CVPS ≤6 in predicting fetal adverse outcomes. The summary sensitivity was 0.34 (95% CI, 0.20–0.51), with individual sensitivities ranging from 0.25 to 1.00. The summary specificity was 0.96 (95% CI, 0.92–0.99), with individual specificities ranging from 0.86 to 1.00. Both pooled estimations showed significant heterogeneity (sensitivity: $p = 0.0001$, $X^2 = 18.19$, $I^2 = 89.0\%$; specificity: $p = 0.0006$, $X^2 = 14.89$, $I^2 = 86.6\%$). The pooled DOR and the SROC curves based on summary sensitivity and specificity across all data sets are shown in Table 2. The pooled DOR was 17.74 (95% CI, 1.28–246.42), with individual DORs ranging from 2.00 to 96.43. The results of DOR showed no consistency across the included reports, with noticeable heterogeneity ($p = 0.0520$, Cochran-$Q = 5.91$, $I^2 = 66.2\%$). The point size in the SROC curve represented the proportional study weight. Most data gathered near the top left corner where sensitivity and specificity were both the
Table 1. Main characteristics of included studies.

| Author         | Year | Type of studies | Regions | Ultrasound system | Study cohort                                      | Treatment in vitro | Fetus with adverse outcome | No. and mean CVPS | Treatment in vitro | Fetus with common outcome | No. and mean CVPS | Cut-offs of CVPS |
|----------------|------|-----------------|---------|-------------------|---------------------------------------------------|-------------------|-----------------------------|-------------------|-------------------|------------------------|-------------------|------------------|
| Hofstatter [9] | 2006 | RS, USA         | Acuson 128XP system | USA        | Fetal hydrops | 48 (5.5 ± 1.2, 6.3 ± 1.5) | No                  | No                           | -                 | No                | -                      | -                 | 6                |
| Makikallio [26] | 2008 | RS, Finland     | Acuson Sequoia C512 system | Finland       | Intrauterine growth restriction | 7 (4.5 ± 1.2) | 25 (6.0 ± 1.5) | 6, 7 and 8 | No               | -                      | -                 | 8                |
| Shah [24]     | 2008 | RS, USA         | Acuson Sequoia C512 system | USA        | Twin-twin transfusion | – | – | – | No | – | – | – |
| Wieczorek [23] | 2008 | RS, USA         | Acuson Sequoia C512 system | USA        | Fetal congenital heart defects | 26 (8.1 ± 1.2, 8.8 ± 0.9) | 103 (8.8 ± 0.9) | 6, 7 and 8 | No | - | - | 7 and 8 |
| Byrne [19]    | 2011 | RS, USA         | Acuson Sequoia C256 and C512 ultrasound systems | USA        | Sacrococcygeal teratoma and twin-reversed arterial perfusion | 6 (8.1 ± 1.4, 8.7 ± 0.8) | 11 (9.9 ± 0.3) | 7 and 8 | No | 8.7 ± 1.2 | 9 (7.8 ± 0.3) | - |
| Arunamata [16] | 2012 | RS, USA         | Acuson Sequoia C512 system | USA        | Fetal left ventricular noncompaction | 12 (6.1 ± 1.2) | 3 (7.7 ± 0.6) | - | No | - | - | - |
| Statile [15]  | 2012 | RS, USA         | Acuson Sequoia C512 or S2000 ultrasound systems | USA        | High cardiac output lesions | 8 (7.0 ± 2.3) | 21 (8.6 ± 2.0) | - | 6, 7 and 8 | - | - | - |

CVPSc, the cut-offs of CVPS means an exact predictor for adverse outcome of fetus.

RS, retrospective study; CVPS, cardiovascular profile score.

Sensitivity analysis

We systematically removed one data set at a time and recalculated the DOR and AUC values for the remaining studies. These results indicated that no single data set carried enough weight to significantly influence the pooled test performance reported for the ability of each score of CVPS to identify cases with adverse outcomes. Finally sensitivity analysis of mean CVPS comparison had been removed one data set at a time and the analysis confirmed in both direction
and magnitude of statistical significance the findings of the overall analysis.

### Analysis of variance

The comparison of prediction value among different scores of CVPS had been done by Z test. Among three scores, the CVPS ≤7 and CVPS ≤6 had more prediction value than CVPS ≤8. However, there was no difference between CVPS ≤7 and CVPS ≤6 (Table 3).

### Discussion

This meta-analysis was restricted to the prediction value of CVPS for perinatal adverse outcome based on fetal echocardiography. Fetal echocardiography had been introduced clinical practice since early 1980s [27]. Many studies focused on its effectiveness of detecting fetal heart structural

| Cut-offs of CVPS | Sensitivity      | Specificity   | DOR             | AUC   |
|------------------|------------------|---------------|-----------------|-------|
| CVPS ≤6          | 0.34 (95% CI, 0.20–0.51) | 0.96 (95% CI, 0.92–0.99) | 17.74 (95% CI, 1.28–246.42) | 0.8777 |
| CVPS ≤7          | 0.38 (95% CI, 0.23–0.54) | 0.96 (95% CI, 0.91–0.98) | 16.66 (95% CI, 4.54–61.09) | 0.8728 |
| CVPS ≤8          | 0.58 (95% CI, 0.45–0.70) | 0.64 (95% CI, 0.57–0.71) | 4.10 (95% CI, 1.65–10.22) | 0.7207 |

CVPS, cardiovascular profile score; DOR, diagnostic odds ratio; AUC, area under the summary receiver operating characteristic curves.
reached a lower level of sensitivity around 0.35. While the prediction value among three scan protocols, we conducted a 
evaluation trying to provide clues for methodological indications. According to the SROC evaluation, the CVPS ≤6 and CVPS ≤7 have the better prediction performance with Q* of 0.8081 ± 0.1041 and 0.8032 ± 0.0524, respectively, compared to CVPS ≤8 of 0.6695 ± 0.0515. We identified the cut-offs of CVPS ≤6 and CVPS ≤7 have acceptable diagnostic power, but they both complained with their lower sensitivities, which means many fetus with adverse perinatal outcomes have been missing by these cut-offs. However, they confirmed that the fetus who has been measured a CVPS ≤7 would suffer the adverse outcomes and severe IUGR. From the evaluation of CVPS ≤8, we identified some patients would still get some common outcomes at the CVPS = 8, which leads the predictive efficacy lower than other two protocols.

The majority of fetuses with congenital heart disease and fetal arrhythmia did not develop congestive heart failure or cardiac dysfunction in utero [1,4,37]. Nevertheless, in a considerable proportion of cases, some signs of heart failure appeared and were diagnosed prenatally by fetal echocardiography. To such patients, they might suffer a disappointed perinatal prognosis. Wieczorek et al. [23] and Statile et al. [15] demonstrated that CVPS ≥8 was associated with a good perinatal outcome. Later time in gestation enhanced the predictive accuracy of the CVPS. While Arunamata et al. [16] showed that the average CVPS of patients who died or underwent heart transplantation was 6.08, while the average CVPS of patients who survived was 7.67. So differences were found across the related studies. With the pooled results of this meta-analysis, we confirmed that CVPS ≥8 was associated with a better prognosis than lower CVPS. But it was also identified that there were a median level of mortality as CVPS = 8, and it would raise at a high level of mortality once CVPS dropped from eight. According to this, once abnormalities were recorded in CVPS evaluation, observation should be performed, and if the CVPS ≤7 intervention in utero including the transplacental digoxin treatment or terminate the pregnancy in late gestation should be taken into procedure [38–40]. Even the fetus might suffer worsen prognosis with a CVPS = 8, but such patients still could undergo carefully observation and prepared for optimal and efficacy intrauterine treatment at the same time according to this analysis [3,25]. Moreover, if a fetus had a CVPS = 8, the mother should be informed well and can make a choice to determine whether intrauterine treatment was done. Previous studies also demonstrated that once CVPS decreased, intervention should be performed [41,42]. However, there were evidences showed that majority of fetus can survive with CVPS from eight and nine, so whether such patients should be underwent treatment was still need more researches, especially for specific original diseases.

The limitations of this meta-analysis are: (1) only English publications were included and (2) univariate analysis about the examination weeks and characteristics of original diseases had not been done for the few publications. The potential influence factors analysis might get unconvincing results for few studies, respectively.

In conclusion, the meta-analysis has proven the CVPS is a credible index for predicting fetal adverse outcome during pregnancy with heart dysfunction. Despite inter-study variability, the test performance of CVPS detected by fetal...
echocardiography techniques was impressive and non-consistent under circumstances of methodological changes to predict perinatal adverse outcomes. But none of cut-off demonstrated both acceptable sensitivity and specificity because of the uncontrollable development and survival to fetus in worsen intrauterine condition. Only CVPS ≤6 and CVPS ≤7 have acceptable predictive efficacy without adaptable sensitivities. So once CVPS decrease at eight, the patient should be observed carefully and prepared for optimal and efficacy intrauterine treatment. With the CVPS dropping from seven, treatment is demanded immediately while some cases suffer irreversible cardiac dysfunction facing an abortion.

Declaration of interest
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online
Supplementary Table S1