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Anthropometric Measures After Fontan Procedure: Implications for Suboptimal Functional Outcome

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Abstract

Background—Abnormal height and adiposity are observed after the Fontan operation. These abnormalities may be associated with worse functional outcome.

Methods—We analyzed data from the NHLBI Pediatric Heart Network cross-sectional study of Fontan patients. Groups were defined by height (z-score < −1.5 or ≥ −1.5) and body mass index (BMI z-score ≤ −1.5 or −1.5 to 1.5 or ≥ 1.5). Associations of anthropometric measures with measurements from clinical testing (exercise, echocardiography, MRI) were determined adjusting for demographics, anatomy, and pre-Fontan status. Relationships between anthropometric measures and functional health status (FHS) were assessed using the Child Health Questionnaire.

Results—Mean age of the cohort (n=544) was 11.9±3.4 years. Lower height-z patients (n=124, 23%) were more likely to have pre-Fontan atrioventricular valve regurgitation (p=0.029), as well as orthopedic and developmental problems (both p<0.001). Lower height-z patients also had lower physical and psychosocial FHS summary scores (both p<0.01). Higher BMI-z patients (n=45, 8%) and lower BMI-z patients (n=53, 10%) did not have worse FHS compared to midrange BMI-z patients (n=446, 82%). However, higher BMI-z patients had higher ventricular mass-to-volume ratio (p=0.03) and lower % predicted maximum work (p=0.004) compared to midrange and lower BMI-z patients.

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Conclusions—Abnormal anthropometry is common in Fontan patients. Shorter stature is associated with poorer FHS and non-cardiac problems. Increased adiposity is associated with more ventricular hypertrophy and poorer exercise performance, which may have significant long-term implications in this at-risk population.

Introduction

The Fontan procedure is performed in children with functional single ventricle; the goal is to achieve passive flow through the pulmonary vascular bed with the single ventricle ejecting exclusively to the systemic circulation. Some children and young adults who have undergone the Fontan procedure have experienced long-term morbidity including arrhythmias, thrombosis, stroke, exercise intolerance, ventricular failure and protein-losing enteropathy (1–6).

Abnormal anthropometry, both in height and weight, has also been reported in this population. Cohen et al. found that children who have undergone the Fontan operation are significantly underweight and shorter than the general population and their own siblings and parents (7). This finding was attributed to the abnormal physiology associated with the Fontan procedure. More recently, the prevalence of childhood obesity was assessed in a population of children with congenital heart disease. Pinto et al found that over 25% of children with heart disease; specifically 16% of those children who had the Fontan operation had a BMI >85th percentile at most recent follow-up (8).

We sought to characterize anthropometry in a large cohort of children who have had the Fontan operation. In addition, we sought to determine if abnormal anthropometry in this population impacts functional outcome (as measured by laboratory measures of ventricular performance and functional health status). We hypothesized that measures of functional outcome would be worse in patients with abnormal anthropometry when compared to those with normal anthropometry.

Methods

This study was supported by U01 grants from the National Heart, Lung, and Blood Institute. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. All patients who participated in the Pediatric Heart Network multi-center cross-sectional study of Fontan survivors were included, if both height and weight were measured at the time of enrollment. The Fontan cross-sectional study included consented patients age 6 to 18 years who agreed to participate, underwent the Fontan procedure at one of the seven Pediatric Heart Network centers and had the surgery performed at least six months prior to participation in the study (9). Patients were excluded if they had a medical or psychiatric condition that precluded functional health status testing. The Fontan cross-sectional study was approved by the institutional review boards at all participating institutions.

Patient anthropometry was classified as follows; for height, patients were classified according to height z-score < -1.5 (lower height-z) and height z-score ≥ -1.5 (higher height-z). For weight, patients were classified by Body Mass Index (BMI) z-score as: BMI z-score ≤ -1.5 (lower BMI-z), BMI z-score between -1.5 and 1.5 (midrange BMI-z) and BMI z-score ≥ 1.5 (higher BMI-z). Height and BMI z-scores were calculated using CDC algorithms (10). We chose these cutoffs (-1.5 to 1.5) to be inclusive of borderline cases of abnormal anthropometry as few patients had a BMI z-score of > 2. Thus, a z-score of -1.5 is equivalent to a percentile of 13.4% and a z-score of 1.5 is equivalent to a percentile of 86.6% in a normal distribution of height and weight. This was consistent with previously

published BMI data; children who have undergone the Fontan procedure tend to be less overweight than their counterparts with other forms of congenital heart disease (8).

A medical chart review was performed on all enrolled patients that captured data including demographics, underlying cardiac anatomy, pre-Fontan characteristics, Fontan procedure characteristics, and outcomes during follow-up after the Fontan procedure. Subjects underwent a series of study tests including echocardiogram, exercise stress testing (Bruce cycle protocol), magnetic resonance imaging (MRI), and B-natriuretic peptide (BNP) measurement. Parents of patients filled out the Parent Report form of the Child Health Questionnaire (CHQ) to assess functional health status. The CHQ measured physical health (PHS) and psychosocial (PSS) well-being, (using 11 domain and 2 summary scores) and has been previously validated (11,12). Some patients did not complete all components of testing. Medical history variables (e.g. age at Fontan, race, gender, type of Fontan, length of stay at time of Fontan, pre-Fontan hemodynamics measured by cardiac catheterization, staging using bidirectional Glenn) and non-cardiac health problems (e.g. asthma, orthopedic problems, developmental delay, anxiety/depression) were assessed as potential covariates for study outcomes. (Appendix I).

Statistical analysis

Continuous variables are described as mean $\pm$ standard deviation or median (inter-quartile range). Height and BMI were treated as categorical variables, based on the classification previously described in the methods. Comparisons of continuous outcomes (CHQ summary and domain scores, laboratory test variables) between height subgroups were made using the Student's t-test if normally distributed and the Wilcoxon rank-sum test otherwise. The comparisons among BMI subgroups were made using ANOVA if normally distributed and non-parametric Kruskal Wallis test otherwise. For categorical outcomes (e.g. presence of protein-losing enteropathy), the Fisher exact test was used. All tests of significance were two-sided. A p-value of <0.05 was considered statistically significant.

For associations between functional health status and anthropometry, the analysis included univariate comparisons of functional health status by height and BMI. To determine whether height and BMI z-scores were associated with demographic, anatomic and pre-Fontan measures (which may confound the relationship between the functional outcomes and height or BMI), a backwards stepwise logistic regression was used to eliminate those variables that were unlikely to influence the relationship between anthropometry and functional health status. Multivariable regression analyses was then performed to inform final models for the relationship between functional health status and the height and BMI z-scores, while controlling for the covariates determined at the previous step.

For associations between laboratory tests and anthropometry, multivariable logistic regression analyses were performed. Analyses were performed separately for each of the four tests (exercise, echo, MRI, BNP). Mean imputation of the missing values in the echocardiography dataset was performed before multivariable regression analyses. The multivariable models were fitted with and without adjustment for the covariates. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Of the 546 patients enrolled in the Fontan cross-sectional study, 544 patients had measured height and weight and were included in this study. The mean age of the cohort was 11.9 ± 3.4 years with a mean time since Fontan of 8.4 ± 3.4 years. For the entire cohort, the mean height-z was -0.8 ± 1.3 and the mean BMI-z was -0.6 ± 1.5 .

Lower Height-z

Among the 544 patients, 124 (23%) were identified with lower height-z (<-1.5) indicating shorter stature. Median age (inter-quartile range, years) for children with lower height-z was 11.1 (8.7, 13.8) compared to 9.1 (8.9, 14.7) for those with higher height-z ($p = 0.18$, Wilcoxon rank-sum test). There were no differences between the two groups with regard to exercise stress testing measures. However, only 60% of patients with lower height-z performed exercise testing in contrast to 80% of those with higher height-z (Fisher's exact, $p < 0.001$). Of those patients with lower height-z who did perform the exercise stress test, they were no more likely to have sub-maximal effort (defined as a respiratory exchange ratio < 1.1) than those with higher height-z. On echocardiography, the Tei index was found to be marginally lower in those patients with lower height-z (0.60 ± 0.16 versus 0.64 ± 0.18 , $p = 0.048$; non-parametric Wilcoxon $p=0.053$). No other echocardiographic variables or MRI variables were significantly different between groups. Median BNP was significantly higher in those patients with lower height-z compared to those with higher height-z (16 (interquartile range 8–33) versus 12 (interquartile range 7–25), $p = 0.035$), though still in the normal range in both groups. Twenty patients in the cohort were identified as having protein-losing enteropathy. When evaluated as categorical height-z groups, protein-losing enteropathy was not associated with lower height-z. However, when analyzed as a continuous variable, protein-losing enteropathy was associated with lower height-z (non-parametric Wilcoxon $p < 0.001$).

Both the PHS and PSS summary scores from the Parent Report CHQ forms were significantly lower in the lower height-z group (Table 1). Almost all raw domain scores were also significantly lower in the lower height-z group (Table 1).

Multivariable regression analysis showed that children with the following conditions were more likely to have lower height-z: moderate to severe atrioventricular valve regurgitation prior to the Fontan procedure, behavioral problems and orthopedic problems (Table 2)

Lower and Higher BMI-z

Of the cohort, 53 patients (10%) had a BMI-z <-1.5 (lower BMI-z), 45 patients (8%) had a BMI-z ≥ 1.5 (higher BMI-z) and 446 patients (82%) had a midrange BMI-z (between -1.5 and 1.5). Median age (inter-quartile range, years) for higher BMI-z patients was 12.1 years (10.1, 14.6) compared to 11.3 years (8.9, 14.7) for those patients with midrange BMI-z and 10.2 years (9.4, 13.7) for those patients with lower BMI-z. There was no significant difference in age among the three BMI groups ($p = 0.230$, Kruskal-Wallis rank test); this remained true even for a two-way comparison between the higher BMI-z and lower BMI-z patients ($p = 0.055$, unadjusted for multiple comparisons).

Results of univariate analyses are presented in Table 3. With regard to exercise stress testing, children with higher BMI-z had lower mean values for VO_2 , maximum work rate, VO_2 at anaerobic threshold and maximum systemic oxygen saturation than the other BMI-z groups. For echocardiographic measures, ventricular mass-to-volume ratio was marginally different among BMI-z groups with the highest mean value in those with BMI-z >1.5 ($p=0.027$, non-parametric Kruskal Wallis $p=0.186$). No other differences were found among groups regarding other echocardiographic measures, cardiac MRI measures or BNP levels.

Only % predicted maximum work rate was selected in the final multivariable model for exercise variables: a ten unit increase in % predicted maximum work rate was associated with an increase in the predicted odds of being in the low or midrange BMI-z group by a factor of 2.1–2.2. Ventricular mass-to-volume ratio on echocardiogram was the only variable selected in the final multivariable model for echocardiographic measures: when mass-to-volume ratio increased by one unit, the odds of being in a higher BMI-z group

increased by a factor of 2.4. There was no association between BMI-z and protein-losing enteropathy when assessing BMI-z in categorical groups.

Parent reported CHQ summary scores for both the PHS or the PSS were not significantly different between BMI-z groups. In addition, there were no differences in any of the raw domain scores. Finally, no medical history variables or non-cardiac health problems were significantly different between BMI-z groups.

Discussion

This study establishes a range of anthropometric indices for children and adolescents after the Fontan procedure. Shorter stature (lower height-z) in the Fontan population is particularly common and is associated with worse functional health status as measured by the Parent Report CHQ compared to those who are taller. In addition, shorter children and adolescents are more likely to have non-cardiac problems compared to their normal height counterparts. Thus, lower height-z may be a marker for suboptimal outcome after the Fontan procedure.

In contrast, patients with lower BMI-z do not appear to have worse functional outcome related to their weight. However, those patients with higher BMI-z do have clinical markers that may predict worse outcome including higher mass-to-volume ratio of the ventricle on echocardiography and worse performance on exercise stress testing. This suggests a possible cardiac burden associated with increased weight in this population of patients.

Lower Height-z

Shorter stature (height-z < -1.5) occurred in almost one quarter of the population in this cohort of Fontan survivors, compared to the expected 13.4% in the healthy pediatric population. This finding is similar to others who have reported short height in children after the Fontan procedure (7,13,14). It has been suggested that the chronic hypoxemia experienced by children with single ventricle physiology may result in delayed bone growth and thus short stature. Moreover, children and adolescents with Fontan physiology are known to have lower cardiac output than comparable aged children with two ventricle circulations and this may also affect bone growth, even when the patient is predicted to be taller based on parental height (15).

Importantly, children with shorter stature had significantly worse functional health status as measured by the Parent Reported CHQ. In fact, almost all domains were worse in those patients with shorter stature. This is an interesting finding suggesting that shorter stature may be a surrogate for worse physical and psychological condition in the Fontan population. Indeed, children with shorter stature were more likely to have significant pre-Fontan atrioventricular valve regurgitation (a marker of poor cardiac outcome (16–18)). Moreover, children with shorter stature were more likely to have orthopedic problems and behavioral problems. Orthopedic problems may be the cause of the shorter stature in some cases. In addition, children with behavioral problems may have an undiagnosed genetic disorder that results in growth abnormalities. The association of behavioral issues and orthopedic problems with lower height-z may also explain that significantly fewer patients in the lower height-z group participated in the exercise portion of the study.

Lower BMI-z

Lower BMI-z (10%) in this population of children after Fontan operation is similar to the distribution that would be expected in a normal population of healthy children. We did expect a higher prevalence of underweight than was seen in our cohort. Others have found a higher prevalence of underweight in this population. Prior to the bidirectional Glenn

procedure when the heart is volume overloaded, poor weight gain is common (7,13). Cohen et al. found that the mean z-score for weight in patients with single ventricle physiology about to undergo the bidirectional Glenn procedure was -1.5 , with some improvement to -0.91 after the Fontan procedure (7). However, the weight z-score never normalized in their cohort. Vogt et al. have recently reported similar findings regarding improved but not normalized growth after the bidirectional Glenn procedure (13). They found that systemic to pulmonary artery collaterals were a risk factor for persistent poor growth after the Fontan procedure. The status of systemic to pulmonary artery collaterals was not known in our population.

Interestingly, lower BMI-z was not associated with measurable differences in exercise performance or ventricular performance as measured by echocardiography or MRI. This was somewhat unexpected if one considers that underweight after the Fontan procedure is an indication of poor medical condition and/or feeding disorders. Lower BMI-z was also not associated with poorer functional health status as measured by parent-reported CHQ. However, lower BMI-z was not particularly severe in our cohort and underweight may not have the same psychosocial stigma associated with it as overweight does.

Higher BMI-z

Approximately 8% of children in our cohort had higher BMI-z. Thus, the epidemic of obesity, well recognized in otherwise healthy children has not had a significant impact in children after Fontan operation. A recent study assessing weight in children with congenital heart disease found a higher rate (16%) of overweight and obesity amongst patients with single ventricle who live in Philadelphia and Boston (8). The higher prevalence of overweight in this earlier report may in part be explained by a higher prevalence of obesity in the study cities. In the present study, children with higher BMI-z were found to have worse exercise performance particularly related to predicted work rate. Though the cause of this association is unknown, this finding may be a reflection of sedentary lifestyle and deconditioning in this population. Restriction from certain types of exercise is common for patients who have had the Fontan operation, particularly those on systemic anticoagulation. Formal activity restriction in children with congenital heart disease has been shown to be a predictor of the development of obesity (19). Moreover, Fontan patients generally have very low levels of daily physical activity, but this is only weakly related to exercise capacity (12).

The ventricular mass-to-volume ratio as measured by echocardiography was marginally higher in the children with higher BMI-z compared to the lower weight groups. Increased ventricular mass has been previously reported amongst obese children without congenital heart disease (20,21). Increased ventricular mass-to-volume ratio is of particular concern in the Fontan population with one functional ventricle. Increased ventricular mass suggests that the ventricle must work harder to eject blood to the systemic circulation. In the long-term, ventricular failure may occur earlier in this subset of patients compared to the Fontan patients with BMI within normal range. Cardiac failure is known to occur in obese adults with structurally normal hearts as a result of the hemodynamic burden of the increased weight (22). Overweight is therefore a particularly worrisome finding in patients who have had the Fontan procedure and warrants close follow-up, education and preventive measures.

Despite the findings on cardiac laboratory testing, the parent-reported Child Health Questionnaire did not reveal any differences between the higher BMI-z and other weight groups. This finding was also surprising as previous studies have reported that overweight children without medical problems as well as those with other medical conditions such as asthma have worse reported functional health status than their normal weight counterparts (23–25). There were very few patients in the cohort with severely elevated BMI-z and this may account for the fact that functional health status was not measurably different.

Limitations—There may have been some selection bias in the Fontan cross-sectional study, since the lower age limit for entry was 6 years. A healthier cohort may have been willing to participate in the study. However, this is the largest cohort of patients after Fontan that has been recently reported. The lower BMI-z and higher BMI-z groups were small, decreasing our power to detect differences particularly amongst risk factors of low prevalence. The use of a parent to report functional health status may have inherent bias. Parents tend to report that their children function at a lower level than the children report themselves (26).

Conclusions

Abnormal anthropometry is common after the Fontan procedure. Shorter stature may be a marker of suboptimal physiologic outcome and may negatively impact on the psychosocial outcome and overall quality of life for these patients. Lower and higher BMI are not associated with worse functional health status. However, higher BMI is likely to be poorly tolerated in the long-term secondary to associated risks such as increased afterload and higher ventricular mass. Exercise restriction and sedentary lifestyle may be a detriment to the long-term outcome of children after the Fontan procedure. Preventive cardiology practices need to be developed to address these concerns in order to improve the long-term health of the single-ventricle population (27).

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Appendix 1. Variables considered as potential covariates in analysis

Medical history variables

Age at Fontan

Race

Gender

Stage II surgery performed

Ventricular type

Fontan type

Pre-Fontan systemic O₂ saturation

Age at volume unloading surgery

Pre-Fontan pulmonary artery pressure

Pre-Fontan end-diastolic pressure

Pre-Fontan anatomic diagnosis

Hypoplastic left heart syndrome

Tricuspid atresia

Common atrioventricular valve/heterotaxy/unbalanced atrioventricular canal

Pre-Fontan moderate to severe atrioventricular valve regurgitation

Pre-Fontan moderate to severe ventricular dysfunction

Surgical fenestration of Fontan

Cardiopulmonary bypass time (minutes)

Post-operative complication: prolonged pleural/pericardial effusions/chylothorax

Length of hospital stay for Fontan (days)

Household income

Highest grade of school completed

If child is firstborn

Non-cardiac health problems

Asthma

Non-asthma respiratory problems

Allergies

Orthopedic problems

Sleep problems

Vision problems

Speech problems

Deafness

Anxiety

Depression

Developmental delay

Attention problems

Learning problems

Behavior problems

Figure 1.
Box and whiskers distribution of Physical Health Summary Score (1A) and Psychosocial Summary Score (1B) for height-z groups and BMI-z groups.

Table 1

Comparison of two height groups for parent completed CHQ (Child Health Questionnaire) Summary Scores. Data is reported as median (interquartile range). Raw domain scores are also reported.

CHQ Domain	Height z-score < -1.5	Height z-score ≥ -1.5	P value
N	124	420	
Physical Functioning Summary Score	46.8(32.8, 51.7)	49.8(40.9,54.3)	<0.001
Psychosocial Functioning Summary Score	44.3(36.5,53.5)	49.5(42.3,56.3)	0.001
<i>Domain Raw Scores</i>			
Physical Functioning	83.3(66.7,94.9)	88.9(77.8,100)	<0.001
Freedom from Bodily Pain	100(70.0,100)	80.0(70.0,100)	0.2
General Health	47.5(30.8,55.8)	55.8(42.3,66.7)	<0.001
Self-Esteem	75.0(62.5,91.7)	79.2(62.5,91.7)	0.3
Limits: Physical	100(66.7,100)	100(83.3,100)	<0.001
Mental Health	70.0(60.0,85.0)	80.0(68.8,85.0)	0.01
Limits: Emotional	88.9 (44.4, 100)	100(77.8,100)	<0.001
Parent Impact: Time	77.8(55.6,100)	88.9(66.7,100)	<0.001
Parent Impact: Emotion	50.0(33.3, 75.0)	66.7(41.7,83.3)	<0.001
Behavior	68.3(55.4,83.3)	76.7(64.2,85.0)	0.01

Table 2

Multivariable model assessing predictors of lower height-z (see Appendix 1 for the list; N= 473). Children with the following conditions were more likely to have lower height-z

Variable	Parameter Estimate (SE)	P value	Odds Ratio	95% Confidence Interval
Pre-Fontan moderate/severe atrioventricular valve regurgitation	1.09	0.018	2.98	(1.21, 7.35)
Orthopedic problems	0.88	0.007	2.42	(1.28, 4.58)
Behavioral problems	0.76	0.002	2.14	(1.32, 3.46)

Table 3

Cardiac testing variables assessed for patients in the three BMI groups. All values expressed as mean $\pm$ SD, or median (iqr). VO₂ = oxygen consumption, VAT = ventilatory anaerobic threshold, BP = blood pressure, AVV = atrioventricular valve, TDI = tissue Doppler imaging. P-values are based on t-test (or Kruskal-Wallis if marked with *)

Characteristic	BMI ≤ -1.5	$-1.5 < \text{BMI} < 1.5$	BMI ≥ 1.5	P Value
Exercise Stress Testing				
<i>N</i>	18	137	11	
% Predicted Peak VO ₂	68.2 $\pm$ 12.6	67.9 $\pm$ 14.4	51.9 $\pm$ 15.3	0.002
% Predicted Max Work Rate	68.4 $\pm$ 19.4	67.0 $\pm$ 15.2	50.8 $\pm$ 15.1	0.004
% Predicted VO ₂ at VAT	79.9 $\pm$ 14.7	77.8 $\pm$ 21.7	61.8 $\pm$ 21.2	0.06
% Predicted Max O ₂ Pulse	94.9 $\pm$ 21.3	88.8 $\pm$ 21.7	71.4 $\pm$ 24.3	0.018
Resting Systolic BP (mmHg)	102.93 $\pm$ 17.8	107.9 $\pm$ 13.3	115.6 $\pm$ 12.5	0.06
Echocardiogram				
<i>N</i>	40	341	32	
Ventricular Mass z-score	0.4 $\pm$ 1.6	1.0 $\pm$ 2.3	1.0 $\pm$ 2.3	0.2
Ejection Fraction z-score	-0.7 $\pm$ 1.8	-0.9 $\pm$ 2.1	-0.6 $\pm$ 2.2	0.6
Total Mass to Volume Ratio	1.1 (0.8, 1.3)	1.2 (1.0, 1.4)	1.2 (1.0, 1.6)	0.2*
Tei Index	0.6 $\pm$ 0.1	0.6 $\pm$ 0.2	0.7 $\pm$ 0.2	0.3
Early:Late AVV Velocity:E/A	1.6 $\pm$ 0.6	1.6 $\pm$ 0.6	1.7 $\pm$ 0.6	0.7
Ventricular Flow Propagation	67.7 $\pm$ 21.6	62.9 $\pm$ 20.4	67.0 $\pm$ 16.3	0.6
TDI Peak Early Diastolic Velocity (cm/sec)	9.0 $\pm$ 3.0	9.4 $\pm$ 3.3	9.4 $\pm$ 2.8	0.8
Ratio: AVV E vel/TDI Ea vel	8.9 $\pm$ 3.4	8.5 $\pm$ 4.1	8.6 $\pm$ 3.6	0.9
Magnetic Resonance Imaging				
<i>N</i>	20	157	16	
Total Mass to Volume Ratio	0.8 $\pm$ 0.2	0.9 $\pm$ 0.3	1.0 $\pm$ 0.3	0.2
Total Stroke Volume	57.1 $\pm$ 24.2	66.2 $\pm$ 24.7	67.7 $\pm$ 25.8	0.3
Total Ejection Fraction	57.4 $\pm$ 9.9	57.4 $\pm$ 8.9	51.8 $\pm$ 13.4	0.1
Cardiac Index (L/min/M ²)	4.7 $\pm$ 1.6	5.1 $\pm$ 1.7	5.6 $\pm$ 1.6	0.3
B Natriuretic Peptide (BNP) pg/ml				
<i>N</i>	50	420	39	
BNP	9.5 (6.3, 26.1)	13.4 (7.3, 25.3)	12.2 (6.5, 27.7)	0.8