Canadian Journal of Cardiology 35 (2019) 727–735

Clinical Research

Association of Soluble ST2 Serum Levels With Outcomes in Pediatric Dilated Cardiomyopathy

Hongzhao You, MS,[a,c] Wenxi Jiang, MS,[a] Meng Jiao, MD,[a,b] Xue Wang, MS,[a] Lixin Jia, PhD,[a] Shijie You, MD,[c] Yulin Li, PhD,[a] Haichu Wen, MS,[a] Hongfeng Jiang, PhD,[a] Hui Yuan, MD,[d] Jie Huang, MD,[c] Bokang Qiao, PhD,[a] Ya Yang, MD,[a] Mei Jin, MD,[a,b,*] Yuan Wang, PhD,[a,*] and Jie Du, PhD[a,*]

[a] *Beijing Anzhen Hospital, Capital Medical University; Key Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education; Beijing Collaborative Innovation Centre for Cardiovascular Disorders; Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China*

[b] *Department of Pediatric Heart Centre, Beijing Anzhen Hospital, Capital Medical University; Beijing Pediatric Heart Centre, Beijing, China*

[c] *State Key Laboratory of Cardiovascular Disease, Cardiovascular Institute, Fuwai Hospital and National Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

[d] *Department of Clinical Laboratory, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China*

See editorial by Greenway, pages 692–693 of this issue.

ABSTRACT

Background: Prognosis in patients with pediatric dilated cardiomyopathy (PDCM) is urgently required to identify high-risk patients. Elevated soluble ST2 (sST2) is associated with prognosis in adult patients with heart failure. This study aimed to assess the prognostic value of sST2 in PDCM.

Methods: Ninety-four patients with PDCM were enrolled after admission from 2 centres in China and followed up for adverse events (death, cardiac transplantation, and heart-failure–related rehospitalization). B-type natriuretic peptide (BNP) and sST2 levels were measured.

Results: Over a median of 678 (interquartile range [IQR]: 533-785) days, 28 (29.8%) adverse events occurred. Patients in the highest tertile of sST2 levels had increased risk of short-term (< 6 months) (adjusted hazard ratio [HR]: 8.36, 95% confidence interval [CI],

RÉSUMÉ

Contexte : Il est urgent de pouvoir disposer de facteurs pronostiques de la cardiomyopathie dilatée chez l'enfant (CDE) afin de pouvoir repérer les patients à haut risque. Un taux élevé de ST2 soluble (ST2s) est associé au pronostic chez les patients adultes atteints d'insuffisance cardiaque. Cette étude avait pour but d'évaluer la valeur pronostique du ST2s dans la CDE.

Méthodologie : Quatre-vingt-quatorze patients atteints de CDE ont été recrutés après leur admission dans deux établissements situés en Chine et ont fait l'objet d'un suivi visant à consigner les éventuels événements indésirables (décès, transplantations cardiaques et réhospitalisations imputables à l'insuffisance cardiaque). Les taux de peptide natriurétique de type B (BNP) et de ST2s ont été mesurés.

Résultats : Sur une période médiane de 678 jours (écart interquartile [EIQ], de 533 à 785), 28 (29,8 %) événements indésirables sont

Dilated cardiomyopathy (DCM) is characterized by systolic dysfunction and left ventricular (LV) dilation, with an annual incidence of 0.57 to 1.13 per 100,000 in children < 18 years old.[1,2] Pediatric DCM (PDCM) is one of the most common causes of congestive heart failure and the main cause of cardiac transplantation in children.[3] Registries from the United States, Australia, and Europe have reported transplant-free survival rates from 60% to 75% within 5 years after diagnosis of DCM.[4] Risk-factor analyses have shown that some echocardiographic variables, such as LV dilation and a lower ejection fraction (EF), can discriminate those patients at high risk and predict adverse events. Periodic follow-up echocardiography is recommended for predicting adverse events and surveillance of progression of DCM.[5] Moreover, circulating biomarkers play an important role in prognosis and assessing therapy. High B-type natriuretic peptide (BNP) levels have been identified as an independent predictor for adverse events.[6] However, using

Received for publication November 19, 2018. Accepted February 18, 2019.

*These authors contributed equally.

Corresponding authors: Dr Jie Du, Beijing Anzhen Hospital, No. 2 Anzhen Rd, Chaoyang District, Beijing 100029, China.

E-mail: jiedu@ccmu.edu.cn

Dr Yuan Wang, Beijing Anzhen Hospital, No. 2 Anzhen Rd, Chaoyang District, Beijing 100029, China.

E-mail: wangyuan980510@163.com

Dr Mei Jin, No. 2 Anzhen Rd, Chaoyang District, Beijing 10029, China.

E-mail: jinmeiazyy@sohu.com

See page 734 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.02.016

0828-282X/

1.02-73.52; $P < 0.05$) and long-term adverse events (2 years) (adjusted HR: 4.23; 95% CI, 1.32-13.60; $P < 0.01$) than those in lower tertiles. The C-statistic was increased with addition of sST2 to BNP from 0.697 (95% CI, 0.541-0.852) to 0.812 (95% CI, 0.697-0.939) for short-term and from 0.712 (95% CI, 0.604-0.819) to 0.798 (95% CI, 0.697-0.899) for prediction of long-term adverse events. An intermediate-risk subgroup was identified, and 24% had adverse events. When serial measurements were taken in a nested case-control subgroup, sST2 levels were constantly high in patients with late adverse events (> 6 months) but gradually decreased in nonadverse-event controls compared with 3-month and 6-month baseline levels.

Conclusions: **In patients with PDCM, serum sST2 levels are associated with adverse events and have robust prognostic value. Serial measurements of sST2 could help in managing patients for monitoring outcomes of treatment.**

survenus. Les patients se situant dans le tertile supérieur des taux de ST2s présentaient un risque accru d'événement indésirable à court terme (< 6 mois) (rapport des risques instantanés [RRI] ajustés 8,36, intervalle de confiance [IC] à 95 %, de 1,02 à 73,52; $p < 0,05$) et à long terme (2 ans) (RRI ajusté, 4,23; IC à 95 %, de 1,32 à 13,60; $p < 0,01$) par rapport à ceux des tertiles inférieurs. La discrimination évaluée par analyse de statistique C augmentait avec l'ajout de ST2s au BNP de 0,697 (IC à 95 %, de 0,541 à 0,852) à 0,812 (IC à 95 %, de 0,697 à 0,939) pour la prédiction des événements indésirables à court terme, et de 0,712 (IC à 95 %, de 0,604 à 0,819) à 0,798 (IC à 95 %, de 0,697 à 0,899) pour celle des événements indésirables à long terme. Un sous-groupe à risque intermédiaire a été constitué, dans lequel 24 % des participants ont présenté des événements indésirables. Lorsque des mesures sérielles ont été prises dans un sous-groupe cas-témoin emboîté, les taux de ST2s étaient systématiquement élevés chez les patients ayant eu des événements indésirables tardifs (> 6 mois), mais diminuaient graduellement chez les témoins sans événement indésirable comparativement aux taux à 3 mois et à 6 mois par rapport à leur valeur au début de l'étude.

Conclusions : **Chez les patients atteints de CDE, le taux sérique de ST2s est associé à la survenue d'événements indésirables et possède une valeur pronostique robuste. Les mesures sérielles du taux de ST2s pourraient faciliter la prise en charge des patients en permettant de suivre les résultats du traitement.**

BNP alone is insufficient for monitoring disease progression or guiding pharmacological treatment.[7] Several candidate biomarkers have emerged as strong tools to predict adverse events in adult DCM,[8] but their prognostic value in childhood remains unknown. Therefore, identification of more specific biomarkers is required to distinguish patients at highest risk of death from those likely to recover and to monitor progress of treatment.

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor family and has 2 isoforms: the membrane-bound isoform (ST2L) and soluble isoform (sST2). *In vitro* studies have reported that the source of circulating sST2 in cardiac diseases is cardiomyocytes responding to biomechanical overload.[9] However, a recent study reported that endothelial cells could also secrete sST2, which was related to diastolic load.[10] Baseline sST2 levels are strong predictors in heart failure at the chronic and acute stages,[11] independent of BNP levels. In adults, sST2 is an independent risk factor for adverse events in patients with DCM and acute heart failure[12] and an independent predictor in clinically stable patients.[13] However, the prognostic value of sST2 in pediatric patients with DCM remains unknown.

Therefore, in this study, we investigated whether serum sST2 could distinguish pediatric patients at high risk of death from those who are likely to recover.

Material and Methods

Study population

An Integrative-Omics Study of Cardiomyopathy Patients for Diagnosis and Prognosis in China (AOCC) is a double-centre, observational, prospective, integrative omics study, which aimed to determine the diagnostic and prognostic value of novel biomarkers in cardiomyopathy. All children (< 18 years old), including patients and 47 healthy controls, were enrolled in Beijing Anzhen Hospital and Fuwai Hospital from September 2015 to March 2017. Figure 1 shows a flowchart of the study. All potential patients were classified first in outpatient departments, according to clinical presentations, imaging results, and laboratory examinations. DCM and heart failure were diagnosed and identified by at least 3 experienced cardiologists. DCM was defined as the presence of 2 or 3 of the following criteria: (1) symptomatic heart failure, (2) LV or biventricular systolic dysfunction, and (3) dilatation that was not explained by abnormal loading conditions or abnormalities of the coronary arteries. Systolic dysfunction was defined by abnormal LV fractional shortening (≤ 25%). LV dilatation was defined by a LV end-diastolic volume or diameter > 2 standard deviations (SDs) from normal according to normograms (z scores > 2) corrected by body surface area and age.[14] Exclusion criteria were as follows: presence or history of systemic disease, such as diabetes, uremia, rheumatic fever, Kawasaki disease, hypertension, or congenital cardiovascular malformations; with a toxic exposure known to cause heart muscle disease (anthracyclines, mediastinal radiation, iron overload, or heavy metal exposure); bedridden for >3 months and/or unable to stand alone (age > 2 years); survival < 30 days; previous history of chronic liver disease or alanine aminotransferase levels > 80 U/L; and a previous history of renal dysfunction. All patients had follow-up visits every 3 months. Follow-up data were prospectively obtained from medical records, communication with the patients' physicians, phone follow-ups, and patients' regular visits to staff physicians at outpatient clinics.

The study was designed and carried out by following the principles of the Declaration of Helsinki. The study was approved by Beijing Anzhen Hospital/Fuwai Hospital Ethics Committee, and all informed consents were obtained. More details are presented at ClinicalTrials.gov (NCT03076580).

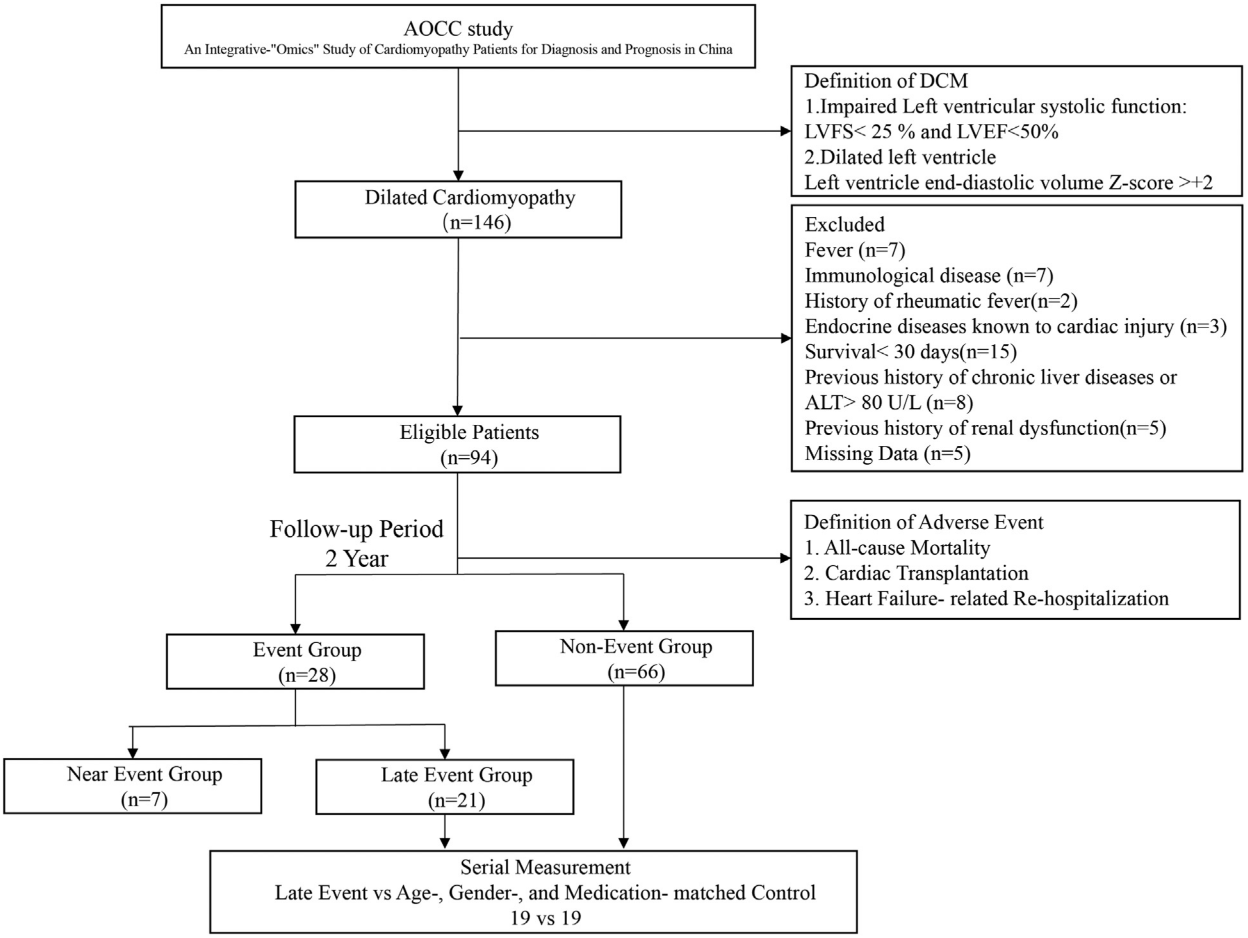

Figure 1. Study design. All patients were followed up for disease outcomes. ALT, alanine aminotransferase; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening.

Data collection

Blood samples were collected from participants with empty stomachs and drawn into sterile polyolefin resin tubes with coagulant. The samples were then centrifuged at 3000 rpm for 10 minutes in the clinical laboratory. The supernatant serum was quickly removed, aliquoted, and stored at −80°C (−112°F). The serum samples were stored at −80°C for < 2 years before analysis. All data were extracted and identified from electronic health records. Laboratory data, transthoracic echocardiography, and sample quantification were recorded and time stamped, as previously described.[15]

Measurement of sST2 levels

Circulating sST2 levels were measured by a high-sensitive sandwich immunoassay (Critical Diagnostics, San Diego, CA). BNP levels were measured by a fluorescence immunoassay using the Triage Meter (Alere, Inc, San Diego, CA). Detailed information of these 2 assays has been reported previously.[16,17] More details are described in Supplementary File 1.

Statistical analyses

Values are expressed as mean ± SD or median (interquartile range [IQR]: Q1-Q3). Demographic characteristics are presented as mean ± SD or percentage as appropriate. Differences between patient groups were evaluated by the χ^2 test for discrete clinical variables and by the Students' *t*-test for continuous variables. Follow-up data were collected as scheduled, and dropouts were excluded. Cox regression analysis was used to determine prognostic predictors of predefined adverse events (death/heart transplantation/heart-failure−related rehospitalization), with proportional hazard assumptions tested after adjusting for covariates. The prognostic value of sST2 against events was determined with receiver operating characteristic curves. Kaplan−Meier plots were used to illustrate events from the time of sampling in relation to sST2 levels. Analyses were performed with SPSS 21.0 (IBM, Chicago, IL) and R version 3.4.0 (R Core Team, Vienna, Austria). All the tests were two-sided, and a *P* value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study patients

A total of 146 eligible perspective pediatric patients with DCM were enrolled in the AOCC clinical cohort. Of them, 94 patients were eventually entered in our study after exclusion (Fig. 1). Overall, 60.2% were female; these patients' median age was 22.0 months (IQR: 10.5-69.5 months), and median LVEF was 38% (IQR: 32%-44%). Serum sST2 levels of patients are shown in Supplemental Fig. S1, with a median level of 23.7 ng/mL. Levels of sST2 were significantly higher in 94 patients with DCM than in age- and sex-matched healthy controls (30.3 ± 18.1 ng/mL vs 14.4 ± 7.5 with $P < 0.001$, Supplemental Table S1). Baseline characteristics of the 94 patients with DCM are presented according to tertiles of serum sST2 levels. Levels of sST2 gradually increased with age (P value for trend = 0.033, Table 1), but previous studies have shown that age does not affect sST2 levels as a confounding factor.[18] During a median follow-up of 678 days (IQR: 533-785 days), 28 patients had all-cause death (n = 6), cardiac transplantation (n = 3), and rehospitalization for heart failure (n = 19). Significantly higher BNP levels and LV dilation were found in patients with adverse events (BNP, P = 0.002; left atrial end diastolic diameter [LVEDD], P = 0.024), with no difference in LVEF, compared with those without adverse events (Table 2).

Association of serum sST2 levels with adverse events in PDCM

We first defined short-term adverse events as all-cause death, cardiac transplantation, or/and heart-failure−related readmission that occurred within 6 months of enrollment. Patients with higher baseline sST2 levels were more likely to experience adverse events in the ensuing 6-month and long-term period (Fig. 2A). A Kaplan−Meier curve showed that patients with PDCM in the highest tertile of baseline sST2 levels had increased risk of adverse events compared with patients in the lower tertiles (log rank test, $P < 0.001$) (Fig. 2B).

To examine whether serum sST2 levels predict short-term and long-term adverse events, adjustments were made with established risk factors (age, sex, z score of LVEDD, LVEF, use of β-blockers, and a previous history of acute heart failure). Following adjustments, elevated serum sST2 levels remained significant predictors of adverse events in the short term (highest tertile, odds ratio [OR] = 8.36, 95% confidence interval [CI], 1.094-73.52, P = 0.044) and long-term periods (highest tertile, hazard ratio [HR] = 4.23, 95% CI, 1.32-13.60, P = 0.015) (Fig. 2C).

Biomarker-based risk stratification of patients with PDCM

Elevated BNP levels are independent predictors for adverse events in pediatric patients with DCM . We determined whether sST2 could be an improvement of traditional biomarkers for predicting short- and long-term adverse events. The receiver operating characteristic curves for 6-month and 3-year adverse events are shown in Supplemental Fig. S2. Addition of sST2 to BNP improved the C-statistic from 0.697 (95% CI, 0.541-0.852, $P < 0.0001$) to 0.818 (95% CI, 0.697-0.939, $P < 0.0001$). The net reclassification improvement (NRI) was 0.204 (95% CI, 0.048-0.375), and the Integrated Discrimination Improvement (IDI) also showed corresponding improvement. For the long-term follow-up period, addition of sST2 to BNP also improved the C-statistic from 0.712 (95% CI, 0.604-0.819, $P < 0.0001$) to 0.811 (95% CI, 0.707-0.899; $P < 0.0001$). The NRI was 0.108 (95% CI, 0.091-0.289), and IDI was 0.026 (95% CI, 0.002-0.079).

To translate these findings into a biomarker-based risk-assessment strategy for long-term adverse events, we stratified patients by BNP and sST2 levels to further subdivide these categories. An sST2 level of 27.7 ng/mL was identified as the cutoff value on the basis of the tertiles of sST2. BNP

Table 1. Baseline characteristics of pediatric dilated cardiomyopathy patients by tertile of serum sST2

	Lowest tertile (≤ 21.1 ng/mL)	Middle tertile (21.2-27.6 ng/mL)	Highest tertile (≥ 27.7 ng/mL)	P value	P value for trend
Age, months	34.2 ± 34.4	49.2 ± 48.9	62.0 ± 65.7	0.100	0.033*
Male	18 (58.1)	10 (32.3)	10 (31.3)	0.121	0.068
Previous history of heart failure, %	15 (48.4)	8 (25.8)	11 (34.4)	0.299	0.396
Echocardiographic measurements at enrollment					
LVEF raw, %	39.3 ± 7.6	37.5 ± 8.1	36.9 ± 6.1	0.383	0.188
LV fraction shortening raw, %	18.4 ± 4.1	18.7 ± 4.4	17.9 ± 3.4	0.604	0.355
LVEDD, z score	4.84 ± 1.52	4.13 ± 1.59	4.64 ± 1.94	0.239	0.645
Septal thickness, z score	−1.27 ± 1.14	−0.93 ± 1.31	−1.06 ± 1.39	0.579	0.523
LV posterior wall thickness, z score	−1.14 ± 1.04	−0.99 ± 1.09	−0.76 ± 1.07	0.369	0.162
Laboratory data					
HDL cholesterol, mmol/L	1.42 ± 0.53	1.33 ± 0.30	1.27 ± 0.46	0.497	0.242
LDL cholesterol, mmol/L	2.70 ± 1.22	2.50 ± 0.82	2.71 ± 1.51	0.778	0.993
Total cholesterol, mmol/L	4.59 ± 1.39	4.16 ± 0.84	4.43 ± 1.86	0.512	0.668
Creatinine, μmol/L	30.99 ± 12.04	33.08 ± 11.22	32.44 ± 14.89	0.206	0.186
Urea, μmol/L	4.47 ± 2.03	4.25 ± 0.96	4.50 ± 1.57	0.809	0.932
Glucose, mmol/L	4.87 ± 0.58	4.94 ± 0.48	4.83 ± 0.55	0.709	0.736
BNP, pg/mL	325.3 ± 370.2	411.5 ± 597.4	485.8 ± 567.4	0.486	0.218
C-reactive protein, μmol/L	1.56 ± 3.99	0.83 ± 2.04	2.11 ± 5.21	0.495	0.596
Medication					
Digoxin	30 (96.8)	26 (83.9)	28 (87.5)	0.289	0.333
Diuretics	27 (87.1)	25 (80.6)	27 (84.4)	0.837	0.568
β-Blocker	18 (58.1)	11 (35.5)	11 (34.4)	0.223	0.122
ACEI	28 (90.3)	24 (77.4)	27 (84.4)	0.854	0.956
Aldosterone antagonist	16 (48.5)	10 (33.3)	13 (41.9)	0.475	0.584

Values are mean ± SD

ACEI, angiotensin-converting enzyme inhibitors; BNP, B-type natriuretic peptide; DCM, dilated cardiomyopathy; EDD, end-diastolic dimension; EF, ejection fraction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; sST2, soluble ST2.

* $P < 0.05$ is significant.

Table 2. Baseline characteristics of pediatric DCM patients with or without adverse events

	Patients with adverse events (n = 28)	Patients without adverse events (n = 66)	*P* value
Age, months	52.5 ± 58.5	46.1 ± 48.7	0.598
Male, %	8 (28.6)	30 (45.5)	0.169
Previous history of heart failure	13 (46.4)	21 (31.8)	0.178
Type			0.436
Idiopathic	18 (64.3)	51 (77.3)	
Myocarditis	4 (14.3)	8 (12.1)	
Familiar	4 (14.3)	6 (9.1)	
Error of metabolism	1 (3.6)	1 (1.5)	
Neuromuscular diseases	1 (3.6)	0 (0)	
Echocardiographic measurements at enrollment			
LV ejection fraction raw, %	38.0 ± 7.4	39.2 ± 7.9	0.410
LV fraction shortening raw, %	18.8 ± 4.6	20.5 ± 3.7	0.257
LVEDD, *z* score	5.23 ± 1.84	4.25 ± 1.57	0.024*
Septal thickness, *z* score	−1.12 ± 1.32	−1.07 ± 1.27	0.975
LV posterior wall thickness, *z* score	−0.89 ± 1.19	−0.99 ± 1.02	0.752
Laboratory data			
HDL cholesterol, mmol/L	1.30 ± 0.56	1.36 ± 0.40	0.154
LDL cholesterol, mmol/L	3.04 ± 1.70	2.49 ± 0.93	0.229
Total cholesterol, mmol/L	4.85± 2.03	4.24 ± 1.08	0.233
Creatine, µmol/L	34.4 ± 15.5	31.2 ± 1.41	0.530
Urea, µmol/L	4.41 ± 1.99	4.40 ± 1.41	0.732
Glucose, mmol/L	4.85 ± 2.02	4.89 ±0.54	0.655
Sodium, mmol/L	137.1 ± 2.3	137.2 ± 2.4	0.810
BNP, pg/mL	546.6 ± 516.0	345.9 ± 508.7	0.002
C-reactive protein, µmol/L	2.64 ± 5.99	1.06 ± 2.75	0.416
sST2 (ng/mL)	40.25 ± 25.97	26.09 ± 11.20	< 0.001
Medication			
Digoxin	22 (78.6)	62 (93.9)	0.309
Diuretics	25 (89.3)	53 (80.3)	0.113
β-Blocker	14 (50.0)	26 (39.4)	0.342
ACEI	25 (89.3)	63 (95.5)	0.882
Aldosterone antagonist	12 (42.9)	27 (40.9)	0.861

Values are mean ± SD.

ACEI, angiotensin-converting enzyme inhibitors; BNP, B-type natriuretic peptide; DCM, dilated cardiomyopathy; EDD, end-diastolic dimension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; sST2, soluble ST2.

* $P < 0.05$ is significant.

(cutoff value set at 140 pg/mL[19]) had a better negative predictive value than did sST2 (0.91 vs 0.87) when BNP was used as the initial classification step. None of the low-risk patients had a 6-month adverse event (Supplemental Fig. S3). In the second classification step, patients were subdivided according to sST2 levels. Patients with high sST2 levels, but low BNP levels, were classified as intermediate—high risk. In patients with elevated BNP levels, sST2 levels ≤ 27.7 ng/mL were used to classify 40 (42.5%) patients at intermediate—low risk (Fig. 3). Compared with the single biomarker strategy, more patients were categorized as intermediate risk. Patients who were classified as intermediate—low risk (10 patients [10.6%]) or intermediate—high risk (40 patients [42.6%]) had similar rates of long-term adverse events. Therefore, our new risk-assessment strategy had the potential to provide a more precise stratification.

Serial sST2 measurements in a nested case-control subgroup

Levels of sST2 are useful for prognosis and monitoring treatment in acute heart failure. To avoid the confounding bias of children's development, we evaluated the change in sST2 levels and its prognostic value in a nested case-control study. Along with 7 pediatric patients with DCM and short-term adverse events, 21 patients had adverse events after 6 months since enrollment ("late adverse events"). Nineteen of these patients had baseline, 3-month, and 6-month serial sST2 measurements. Nineteen age-, sex-, and medical medication-matched patients without adverse events were selected as the control group (Supplemental Table S2). Compared with 3-month and 6-month serum sST2 levels, sST2 levels were constantly higher in patients with adverse events. However, sST2 levels gradually decreased in the nonadverse-event controls (Fig. 4). Moreover, the differences between 3 and 6 months were greater, although baseline level differences were moderate ($P = 0.05$). Notably, 63% of the patients with adverse events had a tendency of a U-shaped sST2 pattern preceding the occurrence of events. However, when sST2 levels were decreased during follow-up, 80% of the patients remained event free. In addition, the sST2 6-month/baseline ratio was a factor for adverse events, independent of BNP (OR = 5.20, 95% CI, 1.01-26.77, $P < 0.05$). These findings suggested that sST2 levels could be used to monitor the progress of DCM treatment.

Discussion

In this study, we showed that sST2 levels were associated with clinical outcome in pediatric patients with DCM. Elevated baseline sST2 levels were strongly associated with adverse events, especially in short-term follow-up. In addition,

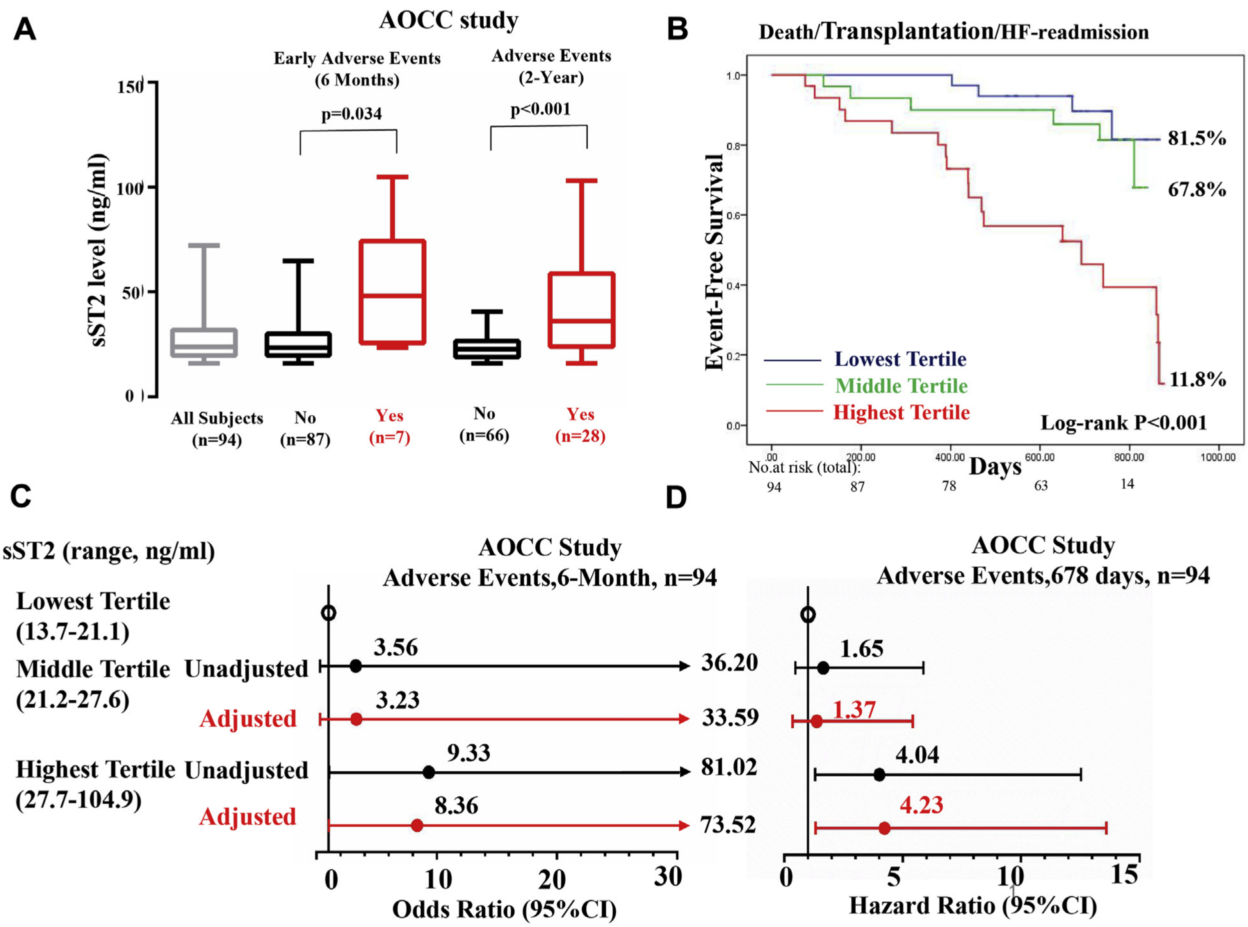

Figure 2. Association of sST2 levels with adverse events in pediatric patients with dilated cardiomyopathy (DCM). (**A**) Box and whisker plots of sST2, soluble ST2 (sST2) levels among pediatric patients with DCM with (Yes) and without (No) adverse events (all-cause death, cardiac transplantation, and heart failure [HF] over the follow-up period). (**B**) Kaplan—Meier estimate value and the risk of adverse events ranked by tertiles of sST2 levels. (**C, D**) Forest plots indicating the risks of incident major adverse cardiac events (MACE) at 6 months and at the end of follow-up according to quartiles of sST2 levels. The multivariable logistic regression model for odds ratios or multivariable Cox model for hazard ratios included adjustments for age, sex, *z* score of left ventricular end-diastolic dimension, left ventricular ejection fraction, use of β-blockers, and a previous history of acute heart failure. The 5% to 95% confidence interval (CI) is indicated by line length. AOCC, An Integrative-Omics Study of Cardiomyopathy Patients for Diagnosis and Prognosis in China.

sST2 could significantly improve on BNP for predicting adverse events. Compared with a sex-, age-, and medical medication-matched subgroup, we found that constant high sST2 levels indicated worse prognoses.

Distinguishing patients at high risk for adverse events from stable patients is clinically relevant.[20] Imaging and biomarkers are promising for distinguishing these patients, including a lower EF and enlarged ventricular dilation, and these are recognized as established risk factors for DCM.[21] Serial NT-proBNP measurement can predict cardiac death.[14] However, upregulation and secretion of BNP levels occur after chronic stimulation through interaction of the myocardium with the neurohormonal or immunological systems in heart failure.[22] Therefore, BNP is not sensitive for pathological changes in the early stage of cardiomyopathy. Identification of specific biomarkers for prognosis and risk stratification is important for clinical decision making. Soluble ST2 is a promising marker associated with several cardiovascular diseases such as heart failure, atrial fibrillation, and aortic dissection. Soluble ST2 is currently recognized as an important adjunct for prognosis and monitoring, and it was included in the 2017 American College of Cardiology/American Heart Association update of heart failure guidelines.[23] Our study showed an association of sST2 levels with 6-month and long-term adverse events. Moreover, sST2 could improve on BNP for predicting adverse events. A combination of BNP and sST2 could discriminate more high-risk patients, and these patients may benefit from early intervention. Therefore, sST2 is a novel biomarker that is superior for identifying pediatric patients with DCM at relatively high risk compared with using BNP alone. Using this strategy, 23 of 94 (24.5%) patients who had 2 negative biomarkers were classified as low risk, and none of them had adverse events in our study. More importantly, approximately 10.6% of the population had low BNP levels but high sST2 levels. Therefore, this part of the population was classified as low risk by conventional stratification but at an increased long-term risk on application of

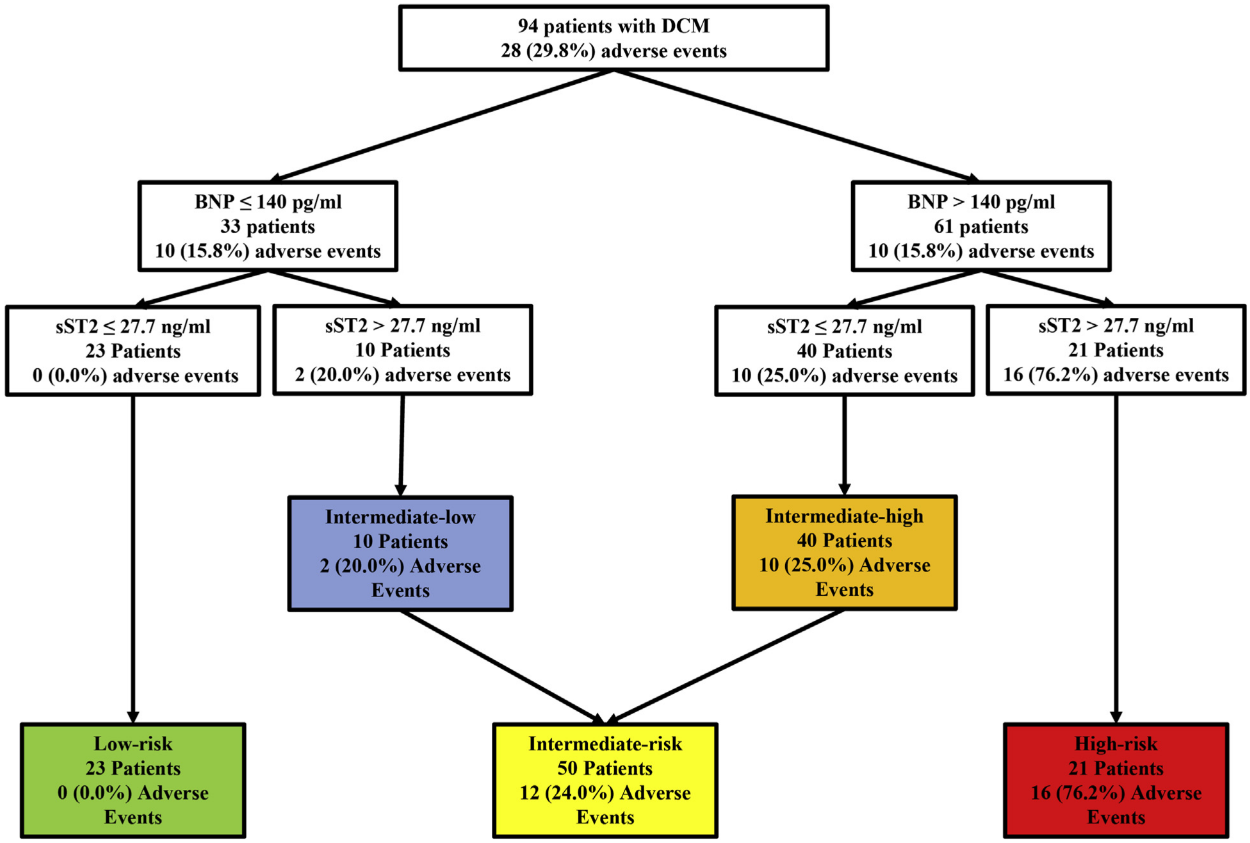

Figure 3. Risk assessment strategies of patients with pediatric dilated cardiomyopathy (DCM). The number (%) of patients with adverse events is shown for each step. Cutoffs were applied at sST2 = 27.7 ng/mL (highest tertile) and B-type natriuretic peptide (BNP) = 140 pg/mL. sST2, soluble ST2.

biomarker-aided stratification. This risk-assessment strategy has the potential to provide a new approach for clinical decision making for aggressive intervention in pediatric patients with DCM and relatively low BNP levels.

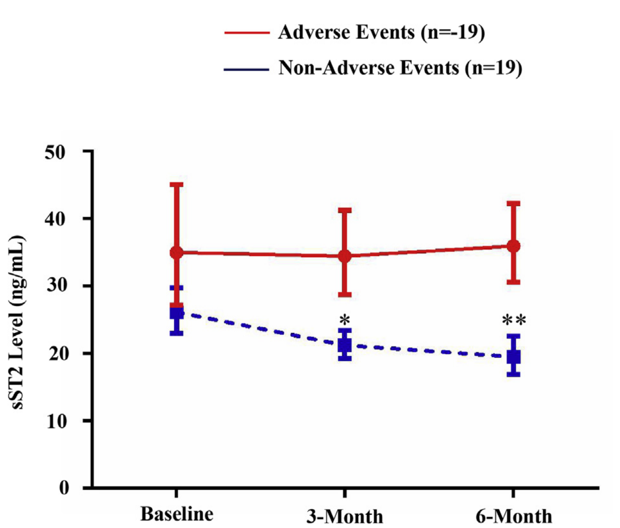

Figure 4. Change in serum soluble ST2 (sST2) levels after 3 and 6 months. Serum sST2 levels at baseline and after 3 months in a subgroup of 19 late adverse events and 19 age-, sex-, and medical medication-matched controls. $*P < 0.05$, $**P < 0.01$.

Fibrosis is one of the most important pathological processes of heart failure or dilated cardiomyopathy. The signalling molecule sST2 may reflect the pathological processes of DCM. sST2 may increase before structural or homodynamic changes and have the potential to be used to assess progression of disease because they play an important role in fibrosis.[11] In our study, we found that serial sST2 measurements were useful in monitoring disease progression compared with a single measurement, and repeated sST2 could reflect progression of pathophysiological processes more accurately. Because of the low coefficient of variation in sST2 levels, sST2 may be suitable for therapeutic monitoring.[24]

Study limitations

There are some limitations in this study. First, although AOCC was a double-centre, prospective, observational study from the 2 largest cardiac disease centres in China, this study is not completely representable for the average DCM population worldwide. With the size of the cohort, identifying the disease-specific reference range value for sST2 and a diagnostic reference range value of sST2 in pediatric patients with DCM is difficult. Therefore, performing further large studies is necessary. Age affects sST2 levels[25] and is an independent risk factor for heart failure. However, in our study, age was not associated with adverse events and did not affect hazard ratios when added as a covariate. We demonstrated a novel and simple biomarker-based risk-assessment strategy that had the potential to provide a more precise stratification for pediatric patients with DCM. However, multicentre validation is necessary to confirm our findings and their translational values. Finally, in subgroup analyses, we included patients with late adverse events (>6 months), and age-, sex-, and medical medication-matched controls, but the sample size was limited. A joint model in a larger multicentre study and more frequent measurements are required to assess the prognostic value of serial sST2 measurements.

Conclusion

This study is the first to show the association between circulating sST2 levels and adverse events in pediatric patients with DCM. Soluble ST2 is a specific biomarker that can distinguish patients at high risk of death from those who are likely to recover. Soluble ST2 has strong prognostic value in short-term and long-term adverse events. In addition, sST2 can improve on BNP for predicting adverse events. Repeated measurement of sST2 could be useful for monitoring disease.

Acknowledgements

We thank Ms Yanyan Zhao from Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College for helping in collection of clinical data and Dr Chunxiao Wu from Xiyuan Hospital, China Academy of Chinese Medical Sciences for technical assistance in data processing. We also thank Dr Xingguang Zhang and Ms Xueyu Han from the Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, for assistance with statistical analysis and Ellen Knapp, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding Sources

This study was supported by grants from the Program for Innovative Research Team (IRT_17R76), National Science Foundation of China (81870341), National Key R&D Program of China (2016YFC0903000), and Beijing Municipal Science and Technology Commission (Z171100000417002).

Disclosures

The authors report no conflicts of interest.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.02.016.