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MATERNAL-FETAL MEDICINE

Placental abruption and long-term cardiovascular morbidity of the offspring

Liron Berkman[1] · Tamar Wainstock[2] · Eyal Sheiner[1] · Daniella Landau[3] · Gali Pariente[1]

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Abstract

Objective While placental abruption is often associated with short-term adverse pregnancy outcomes, we sought to assess whether placental abruption increases the risk for long-term cardiovascular morbidity of the offspring.

Methods To study the long-term cardiovascular hospitalizations of offspring of patients with and without placental abruption, cardiovascular morbidity was assessed up to the age of 18 years according to a predefined set of ICD-9 codes associated with hospitalization of the offspring. Our data consist of deliveries which occurred between the years 1991 and 2014 in a tertiary medical center. Pregnancies following fertility treatments, multifetal pregnancies, and pregnancies with offspring with congenital anomalies, lack of prenatal care, and perinatal mortality were excluded from the study. We used Kaplan–Meier curve to compare cumulative morbidity incidence and Cox proportional hazards model to control for confounder.

Results During the study period, we examined 217,910 deliveries, out of which 0.46% ($n=1003$) were effected by placental abruption. Compared to normal birth children, children born to mothers with placental abruption did not show a significantly higher cumulative incidence of long-term cardiovascular morbidity (1.0% vs. 0.6%; $p=0.127$). Placental abruption was not noted as an independent risk factor for long-term cardiovascular morbidity of offspring in the Cox regression analysis, which adjusted for confounders.

Conclusion Our study does not support the association between placental abruption and risk for long-term cardiovascular morbidity of the offspring.

Keywords Long-term cardiovascular morbidity · Placental abruption · Preterm delivery · Offspring's health

Introduction

Placental abruption is defined as a complete or partial separation of the placenta from the uterine wall prior to delivery. The incidence of placental abruption ranges from 0.4–1% of all pregnancies [1], with an increase in prevalence detected in recent years [2]. The diagnosis of placental abruption is usually made by clinical evaluation. The criteria for diagnosis include painful vaginal bleeding accompanied by tetanic uterine contractions, uterine hypertonicity and abnormal fetal heart rate patterns [3]. Even though placental abruption has a supreme clinical significance, due to its substantial associated morbidity and mortality, there are no proper tests to diagnose or prevent the abruption [4]. Query ID="Q5" Title="We have used the article title given in the title page. Kindly check and confirm if this is fine. Amend if needed."

Placental abruption has a major impact on maternal and perinatal morbidity and mortality. Fetal risks associated with the occurrence of placental abruption are: intrauterine

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Liron Berkman and Tamar Wainstock equally contributed to the article.

✉ Eyal Sheiner
heiner@bgu.ac.il

[1] Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, POB 151, 84101 Beer Sheva, Israel

[2] Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

[3] Department of Pediatrics, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer Sheva, Israel

growth restriction (IUGR), low birth weight, preterm delivery, asphyxia, stillbirth and perinatal death [1–6]. Maternal complications associated with placental abruption include: obstetric hemorrhage, acute renal failure, hysterectomy, disseminated intravascular coagulopathy (DIC) and death [1, 2, 7]. Pariente et al. demonstrated a long-term additional risk for cardiovascular mortality in women with placental abruption [2].

Studies have shown that in women admitted with placental abruption, perinatal mortality was independently associated with preterm delivery [8]. The short-term outcomes of offspring of women with placental abruption are well observed and include respiratory distress, retinopathy of prematurity and patent ductus arteriosus [9, 10]. Long-term complications of offspring include recurrent hospitalizations, neurodevelopment disabilities, growth impairment and impaired lung function [11, 12]. Due to the high survival rates of pre-term infants, the effect on adult health can also be seen. Preterm adults are more likely to have hypertension and vascular changes, insulin resistance and reproductive problems [13, 14].

The short-term association between preterm births, a known complication of placental abruption, and long-term risk of cardiovascular morbidity of offspring has been demonstrated [5]. However, the association between placental abruption and long-term cardiovascular morbidity of the offspring has not been investigated independently of preterm delivery. We hypothesized that placental abruption infants are more susceptible to cardiovascular morbidity during their childhood. The aim of our study is to assess whether children born to mothers with placental abruption have a higher risk of cardiovascular morbidity compared to children of normal pregnancies.

Materials and methods

All women delivering at the Soroka University Medical Center (SUMC), between the years 1991 and 2014 were included in this retrospective cohort study. SUMC is the sole tertiary medical center in the southern region of Israel, which serves the entire population of the region. Thus, the study is based on nonselective population data. The institutional review board, in accordance with the Helsinki declaration, approved the study (SUMC IRB protocol no. 0438-15-SOR).

Placental abruption was defined by the attending physician and International Classification of Disease (ICD) code, using clinical findings such as uterine contractions, vaginal bleeding, fetal distress, abdominal pain, or uterine tenderness [3, 4]. Multifetal pregnancy, children with congenital anomalies or chromosomal abnormalities, pregnancies lacking prenatal care, and perinatal mortality cases were excluded from the analysis.

Offspring of mothers with placental abruption were compared to offspring of mothers without placental abruption. Outcome was defined as cardiovascular-related hospitalization of the offspring up to the age of 18 years, according to predefined set of, ICD-9th edition as detailed in the appendix. Cardiovascular morbidities included were cardiac arrhythmias, endocarditis, hypertension, valvular abnormalities cardiomyopathy, diastolic heart failure, ischemic heart diseases, pulmonary heart diseases and rheumatic fever.

Follow-up was terminated either when the child reached 18 years of age, first hospitalization for cardiovascular etiologies (an event), end of study period or when the child died for non-cardiac reasons.

Data were derived from two databases at SUMC that were crosschecked and merge. The first is the computerized perinatal database, which is recorded directly during and after delivery by the attending physician. To ensure the reliability of the database, experienced medical secretaries routinely reviewed the data before it was entered. Coding is performed after assessing medical prenatal care records together with the routine hospital documents. These procedures are performed to ensure maximal completeness and accuracy of the databases. The second one is the computerized pediatric hospitalization database, which consist of demographic data and medical diagnoses predefined by ICD-9 codes.

Statistical analyses

Statistical analysis was performed using SPSS package 23rd edition (IBM/SPSS, Chicago, IL, USA) as well as the STATA software 12th edition (StataCorp LLC, College Station, TX, USA). Categorical data are shown in counts and rates and the differences were assessed by χ^2 for general associations. *T* test or Man–Whitney *U* tests were used for comparison of continuous variables according to their distribution. Cumulative incidence rates were compared using Kaplan–Meier survival analysis. The log-rank test was used to determine if the differences are significant. Cox regression analysis was conducted to compare cardiovascular-associated hospitalization risk among offspring born to mothers with placental abruption adjusted for duration of follow-up. The model adjusted for potential confounders based on univariable analysis and on the clinical importance of the variables, such as maternal age (years), diabetes, gestational age in weeks, intrauterine growth retardation (IUGR), chronic hypertension and preeclampsia. The final model was chosen based on the best fit and the minimal −2log likelihood. The variables used in the cox regression model were coded as follows: maternal age and gestational age in weeks are continuous, and chronic hypertension, preeclampsia, diabetes, IUGR and preterm delivery are dichotomous. Offspring

born after normal birth (without placental abruption) were considered the reference group. All analyses were two sided; $p < 0.05$ was considered significant.

Results

During the study period, 217,910 deliveries were included, of which 0.46% ($n = 1003$) were complicated with placental abruption. Table 1 summarizes maternal characteristics and immediate perinatal outcomes for both groups. Mothers with placental abruption were older with higher parity order with significantly higher rates of chronic hypertension (3.3% vs. 1.4%, p value < 0.001), preeclampsia (10.2% vs. 4%, p value < 0.001) and preterm births (42.9% vs. 6.2%, p value < 0.001). Cesarean delivery rates were significantly higher in the placental abruption group compared to the control group (75.8% vs. 13.8%, p value < 0.001). Also, rates of IUGR among offspring in the placental abruption group were significantly higher (7.5% vs. 1.9%, p value < 0.001).

Values of umbilical artery blood pH in placental abruption deliveries showed no significant difference between the two groups (7.25 ± 0.16 vs. 7.36 ± 1.03, p value = 0.85).

However, a significant difference in the rates of low Apgar scores at 1st and 5th min was found in offspring of mothers with placental abruption compared to offspring of mothers without placental abruption (27.9% vs. 3.3% and 4.9% vs. 0.3%, for 1st and 5th min, respectively, p value < 0.001).

The comparison between offspring long-term cardiovascular morbidities based on the study group is shown in Table 2. Children born to mothers with placental abruption did not have a significantly higher cumulative incidence of long-term cardiovascular morbidities (p value = 0.13).

In the Kaplan–Meier survival curve, presented in Fig. 1, as compared to offspring born to mothers without placental abruption, those born to mothers with placental abruption did not have a significantly higher risk of cardiovascular morbidity up to the age of 18. Likewise, in the Cox regression analysis after controlling for maternal age, diabetes, gestational age, IUGR, chronic hypertension and preeclampsia, placental abruption was not found to be associated with long-term cardiovascular morbidity of the offspring (Adjusted HR = 1.12, 95% CI 0.60–2.11, $p = 0.71$, Table 3).

Table 1 Demographic and clinical characteristics of women with and without placental abruption

Characteristics	Placental abruption ($n = 1003$)	No placental abruption ($n = 216{,}907$)	OR	95% CI		p value
				Max	Min	
Maternal age, years (mean ± SD)	29.6 ± 6.28	28.2 ± 5.79				< 0.001
Gravidity (%)						
1	18.4	20.6				< 0.001
2–4	41.9	48.4				
5 +	39.7	30.9				
Parity (%)						
1	23.5	24.8				< 0.001
2–4	45.7	51.7				
5 +	30.8	23.5				
Hypertensive disorders of pregnancy (%)	12.3	5.2	2.53	2.09	3.06	< 0.001
Preterm delivery (%)	42.9	6.2	11.29	9.95	12.81	< 0.001
Induction of labor (%)	20	27.6	0.60	0.56	0.70	< 0.001
Cesarean section (%)	75.8	13.8	19.47	16.85	22.51	< 0.001
Gestational age at delivery, weeks (mean ± SD)	36.55 ± 3.55	39.16 ± 1.713				< 0.001
Gender						
Male (%)	53.2	50.9				
Female	46.8	49.1	1.09	0.97	1.24	0.14
Birth weight, grams (mean ± SD)	2630.87 ± 767.38	3324 ± 489.71	1.09	0.97	1.24	< 0.001
Apgar score < 7 at 1 min (%)	27.9	3.3	11.37	9.88	13.07	< 0.001
Apgar score < 7 at 5 min (%)	4.9	0.3	17.84	13.24	24.01	< 0.001
PH (mean ± SD)	7.25 ± 0.16	7. 37 ± 1.04				0.849
Chronic hypertension (%)	3.3	1.4	2.32	1.64	3.30	< 0.001
IUGR (%)	7.5	1.9	4.25	3.348	5.39	< 0.001
Preeclampsia (%)	10.2	4	2.70	2.20	3.30	< 0.001

Table 2 The association between placental abruption and long-term cardiovascular morbidity of the offspring

Offspring long-term cardiovascular morbidity (number)	Placental abruption ($n=1003$)	No placental abruption ($n=216{,}907$)	p value	OR	CI 95%	
Cardiac arrhythmias	2	444	0.66	0.97	0.24	3.91
Peri-myoendocarditis	2	86	0.06	5.03	1.24	20.50
Hypertension	1	155	0.46	1.60	0.22	11.47
Structural valvular abnormalities	0	40	0.83	0.95	0.99	0.99
Diastolic heart failure	0	12	0.94	0.99	0.99	0.99
Ischemic heart diseases	0	4	0.98	0.99	0.99	0.99
Pulmonary heart diseases	0	26	0.88	0.99	0.99	0.99
Rheumatic fever	0	30	0.87	0.99	0.99	0.99
Other	6	632	0.08	2.06	0.92	4.61
Total cardiovascular hospitalization	10	1340	0.12	1.62	0.87	3.02

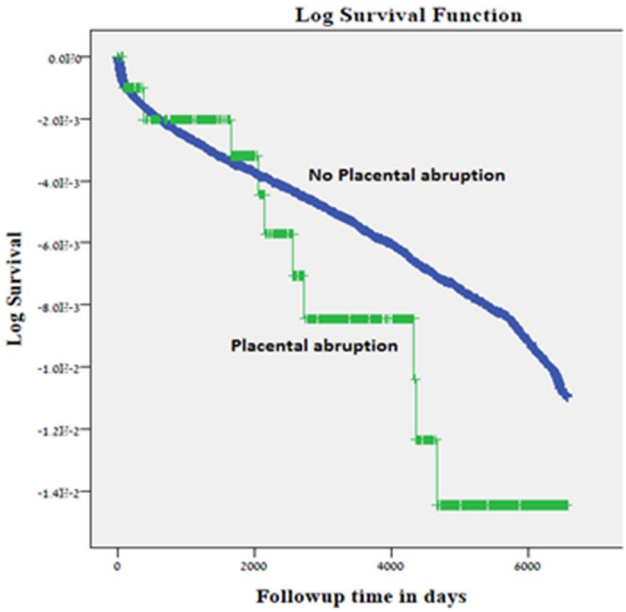

Fig. 1 Kaplan–Meier survival curve demonstrating the cumulative incidence of cardiovascular hospitalizations in infants born to mothers with and without placental abruption (Log rank $p=0.203$)

Discussion

In this population-based analysis of more than 1000 cases of placental abruption, placental abruption was not found to be independently associated with long-term cardiovascular morbidity of the offspring. Crude rates of different cardiovascular disorders were comparable between the groups.

While the association between placental abruption and adverse short-term perinatal outcome is well established, the long-term cardiovascular morbidity of the offspring associated with placental abruption has not been investigated yet. Many studies have shown that placental abruption is independently associated with increased adverse perinatal outcomes such as stillbirth, preterm delivery, low birth weight and lower Apgar scores [10, 15]. Our results also correlate with the above findings, as offspring born after placental abruption in our study had lower Apgar scores at 1st and 5th min, as compared to offspring of mothers without placental abruption. Nevertheless, umbilical artery pH in placental abruption deliveries was not significantly more acidic compered to normal deliveries. These two parameters can be used as a marker to indicate the speed of the delivery

Table 3 Multivariable analysis to predict offspring long-term cardiovascular morbidity

Variables	Adjusted HR	95% CI		p value
		Min	Max	
Placental abruption (vs. none)	1.12	0.60–2.11		0.71
Maternal age (years)	0.99	0.98–1		0.05
Diabetes	1.23	0.99–1.52		0.08
Gestational age (weeks)	0.90	0.88–0.93		<0.001
Chronic hypertension	0.88	0.575–1.353		0.56
IUGR	1.02	0.71–1.46		0.46
Preeclampsia	0.97	0.75–1.26		0.97

(how fast the delivery was indicated) in patients with placental abruption.

The Barker hypothesis of the fetal origins of adult disease was one of the first to establish the association between impaired intra uterine growth and an increased risk for later adult cardiovascular morbidity [16]. Barker et al. suggested that long-term hypertension and cardiovascular disease as an adult could be attributed to fetal programming as an adjustment mechanism used to adapt to the hostile intra-uterine environment.

Different findings in previous studies suggest that the process of placental ischemia may affect the cardiovascular system in various ways. It is believed that the ischemic placenta triggers the release of hypoxia-inducible factors and other placenta-derived factors such as FMS-like tyrosine kinase-1 (sFlt-1) which is a soluble decoy receptor that binds to placental growth factor (PlGF), preventing their interaction with cell-surface receptors on endothelial cells leading to endothelial dysfunction. Concomitantly, there is a downregulation of VEGF molecules that play a major role in inducing nitric oxide formation, which usually neutralizes reactive oxygen species, and vasoconstrictor signaling. The combination of the two results in vasoconstriction state and hypertension [17, 18]. Furthermore, myocardial necrosis with an increase of cardiac-specific enzymes and evidence of DNA breakdown demonstrated by karyolysis and pyknosis are highly suggestive of myocardial cell death that accrues in the cascade of ischemic placenta [19].

These mechanisms might explain the long-term cardiovascular morbidity associated with ischemic placental syndromes such as preeclampsia and preterm delivery.

Kessous et al. found that previous history of preterm delivery was a risk factor for maternal simple and complex cardiovascular morbidity in a follow-up period of more than a decade [20]. An association between in utero exposure to severe preeclampsia and offspring's cardiovascular morbidity such as hypertension, arrhythmia and heart failure has also been demonstrated [21]. These findings may implicate on a similar connection between placental abruption and long-term cardiovascular morbidity since its pathophysiology also relays on the placental ischemia model.

Studies have also demonstrated an association between adverse placental-related perinatal outcomes and cardiovascular-related morbidity such as endocrine and metabolic morbidity in the offspring in association with preterm birth [22], increased risk of cardiovascular-related mortality in pregnancies with growth restriction [23] and an association between low birth weight or preeclampsia and long-term cardiovascular disease [24–26].

Preeclampsia, pre-term delivery, fetal growth restriction and placental abruption [4] are all maternal placental pathologies resulting from placental hypo-perfusion caused by diseased spiral arteries, placental ischemia, and endothelial dysfunction. Hence, we hypothesized that placental abruption will also be associated with long-term childhood cardiovascular morbidity of the offspring, as the damaged endothelium was shown to be related to the metabolic syndrome and was found as an independent predictor of cardiovascular disease [4, 27, 28]. While studies have shown that children born to mothers with preeclampsia and small for gestational age children had early reduced endothelial function, which may have been resulted in later cardiovascular morbidity [29, 30], our study has failed to demonstrate the same association with placental abruption.

The lack of association between placental abruption and long-term childhood cardiovascular morbidity might be due to the fact that we examined only hospitalizations. The information about mild morbidity outside SUMC was not included in the analysis and could influence our results. Another possible explanation to the lack of association in our study relies on the fact that our study examined morbidity of children until the age of 18 and the majority of cardiovascular morbidities usually present later in life [2]. Another explanation for the lack of association is based on the pathophysiology of placental abruption. Although most cases of placental abruption are related to chronic placental disease process, there are other etiologies for placental abruption such as abdominal trauma, rapid acceleration–deceleration of the uterus, uterine abnormalities, cocaine use, and smoking [1, 2, 7, 31]. Those mechanisms are not related to abnormalities in the early development of the spiral arteries and endothelial dysfunction and could divert the results of our study and reduce the long-term risk for cardiovascular morbidity [4, 30, 32–34]

The study's main strength lies on the fact that it is a nonselective, population-based large cohort study that combines databases from the obstetrical department and the entire hospitals records, which allowed us to retrospectively analyze the data to assess the long-term cardiovascular risk. The study was conducted at SUMC, which is a large tertiary medical center that provides obstetric services to the entire population in the southern region of Israel as a sole hospital. Hence, if a woman delivered in SUMC, her child is assumed to come back to the same hospital for any treatment. Another strength of our study is that we used computerized files that were recorded by physicians during the delivery or immediately after it; so, possibility of missing values or recall bias is minimized.

The main limitation of our study lies within its retrospective design. As a population-level analysis, our study can provide evidence only of association and not of causation. Another limitation of our study is the lack of information related to cardiovascular morbidity of the offspring outside SUMC, together with loss to follow-up of women who delivered in SUMC and immigrated from the area.

Nevertheless, one can assume that the rates of immigration are similar between the two groups.

In conclusion, despite the strong association between placental abruption and adverse short-term perinatal outcome, placental abruption does not seem to be associated with long-term cardiovascular morbidity of the offspring. Since the incidence of placental abruption has increased in the last decade, further studies are necessary to determine whether placental abruption is related to long-term chronic morbidities.

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Author contributions BL manuscript writing, LD data collection, PG and SE data management, WT data analysis.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Informed consent No informed consent was needed since identifying details (such as: names, dates of birth, identity numbers and other information) of the participants were not revealed to the researchers at any point.

Appendix

See Table 4.

Table 4 ICD-9 codes used

Groups	Diagnostic code	Diagnosis description
Structural valvular disease	3940	Mitral stenosis
	3949	Other and unspecified mitral valve diseases
	3961	Mitral valve stenosis and aortic valve insufficiency
	3963	Mitral valve insufficiency and aortic valve insufficiency
	3968	Multiple involvement of mitral and aortic valves
	3970	Diseases of tricuspid valve
	4240	Mitral valve disorders
	4241	Aortic valve disorders
	4242	Tricuspid valve disorders, specified as nonrheumatic
	4243	Pulmonary valve disorders
Hypertension	4019	Unspecified essential hypertension
	4372	Hypertensive encephalopathy
	40390	Unspecified hypertensive kidney disease with chronic kidney disease stage I through stage IV, or unspecified
	40391	Unspecified hypertensive kidney disease with chronic kidney disease
	40391	Unspecified hypertensive kidney dis. with chronic kidney disease stage V or end-stage renal disease
	40391	Unspecified hypertensive renal dis. + renal failure
	40591	Unspecified renovascular hypertension
Arrhythmia	4260	Atrioventricular block, COMPLETE
	4263	Other left bundle branch block
	4264	Right bundle branch block
	4267	Anomalous atrioventricular excitation
	4270	Paroxysmal supraventricular tachycardia
	4271	Paroxysmal ventricular tachycardia
	4272	Paroxysmal tachycardia, unspecified
	4273	Atrial fibrillation and flutter
	4275	Cardiac arrest
	4279	Cardiac dysrhythmia, unspecified

Table 4 (continued)

Groups	Diagnostic code	Diagnosis description
	7850	Tachycardia, unspecified
	7851	Palpitations
	42611	First-degree atrioventricular block
	42612	Mobitz (type) II atrioventricular block
	42613	Other second-degree atrioventricular block
	42682	Long QT syndrome
	42689	Other specified conduction disorders
	42731	Atrial fibrillation
	42732	Atrial flutter
	42741	Ventricular fibrillation
	42760	Premature beats, unspecified
	42761	Supraventricular premature beats
	42769	Other premature beats
	42789	Other specified cardiac dysrhythmias
	427811	Sinus bradycardia
	42671	Wolff-Parkinson-White syndrome
Rheumatic fever	390	Rheumatic fever without mention of heart involvement
	3911	Acute rheumatic endocarditis
	3918	Other acute rheumatic heart disease
	3919	Acute rheumatic heart disease, unspecified
	3920	Rheumatic chorea with heart involvement
	3929	Rheumatic chorea without mention of heart involvement
	3941	Rheumatic mitral insufficiency
	3951	Rheumatic aortic insufficiency
	39890	Rheumatic heart disease, unspecified
Ischemic heart disease	414	Other forms of chronic ischemic heart disease
	4100	Acute myocardial infarction of anterolateral wall
	4109	Acute myocardial infarction of unspecified site
	4111	Intermediate coronary syndrome
	4149	Chronic ischemic heart disease, unspecified
	4292	Cardiovascular disease, unspecified
	4295	Rupture of chordae tendineae
	41000	Acute myocardial infarction anterolateral, episode of care unspecified
	41011	Acute myocardial infarction other anterior, initial episode of care
	41071	Acute myocardial infarction subendocardial, initial episode of care
	41091	Acute myocardial infarction unspecified site, initial episode of care
	41410	Aneurysm of heart (wall)
	42979	other, mural thrombus (atrial) (ventricular) acquired, following myocardial infarction
Pulmonary heart disease	4160	Primary pulmonary hypertension
	4168	Other chronic pulmonary heart diseases
	4169	Chronic pulmonary heart disease, unspecified
	4171	Aneurysm of pulmonary artery
	41512	Septic pulmonary embolism
	41519	Other pulmonary embolism and infarction

Table 4 (continued)

Groups	Diagnostic code	Diagnosis description
Perimyoendocarditis	4210	Acute and subacute bacterial endocarditis
	4211	Acute and subacute infectious endocarditis in disease classified elsewhere
	4230	Hemopericardium
	4232	Constrictive pericarditis
	4233	Cardiac tamponade
	4238	Other specified diseases of pericardium
	4239	Unspecified disease of pericardium
	4251	Hypertrophic obstructive cardiomyopathy
	4252	Obscure cardiomyopathy of Africa
	4253	Endocardial fibroelastosis
	4254	Other primary cardiomyopathies
	4257	Nutritional and metabolic cardiomyopathy
	4259	Secondary cardiomyopathy, unspecified
	4289	Heart failure, unspecified
	4290	Myocarditis, unspecified
	42090	Acute pericarditis, unspecified
	42099	Other acute pericarditis
	42290	Acute myocarditis, unspecified
	42291	Idiopathic myocarditis
	42292	Septic myocarditis
	42490	Endocarditis, valve unspecified, unspecified cause
Heart failure	4280	Congestive heart failure
	4280	Congestive heart failure, unspecified
	4281	Left heart failure
	42841	Acute combined systolic and diastolic heart failure
Heart disease not otherwise specified	4299	Heart disease, unspecified
	9971	Cardiac complications, not elsewhere classified
	42989	Other ill-defined heart diseases
Other	7852	Functional and undiagnosed cardiac murmurs
	7852	Undiagnosed cardiac murmurs (heart murmur not otherwise specified)
	7859	Other symptoms involving cardiovascular system
	78521	Systolic murmur

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