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CLINICAL RESEARCH ARTICLE

Cardiovascular outcomes in children with Kawasaki disease: a population-based cohort study

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BACKGROUND: The risk of cardiovascular events after Kawasaki disease (KD) remains uncertain. Our objective was to determine the risk of cardiovascular events and mortality after KD.

METHODS: Population-based retrospective cohort study using Ontario health administrative databases (0–18 years; 1995–2018). Exposure: pediatric KD hospitalizations. Each case was matched to 100 non-exposed controls. Primary outcome: major adverse cardiac events (MACE; cardiovascular death, myocardial infarction, or stroke composite). Secondary outcomes: composite cardiovascular events and mortality. We determined incidence rates and adjusted hazard ratios (aHR) using multivariable Cox models.

RESULTS: Among 4597 KD survivors, 79 (1.7%) experienced MACE, 632 (13.8%) composite cardiovascular events, and 9 (0.2%) died during 11-year median follow-up. The most frequent cardiovascular events among KD survivors were ischemic heart disease (4.6 events/1000 person-years) and arrhythmias (4.5/1000 person-years). KD survivors were at increased risk of MACE between 0–1 and 5–10 years, and composite cardiovascular events at all time periods post-discharge. KD survivors had a lower mortality risk throughout follow-up (aHR 0.36, 95% CI 0.19–0.70).

CONCLUSION: KD survivors are at increased risk of post-discharge cardiovascular events but have a lower risk of death, which justifies enhanced cardiovascular disease surveillance in these patients.

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IMPACT:

- Among 4597 Kawasaki disease (KD) survivors, 79 (1.7%) experienced major adverse cardiac events (MACE) and 632 (13.8%) had composite cardiovascular events during 11-year median follow-up.
- KD survivors had significantly higher risks of post-discharge MACE and cardiovascular events versus non-exposed children.
- Only nine KD survivors (0.2%) died during follow-up, and the risk of mortality was significantly lower among KD survivors versus non-exposed children.
- Childhood KD survivors should receive preventative counseling and cardiovascular surveillance, aiming to mitigate adult cardiovascular disease.

INTRODUCTION

Kawasaki disease (KD) is a common childhood vasculitis, which may result from an immune response to infectious or environmental triggers in genetically susceptible individuals.[1] The global incidence of KD is increasing, as observed in Asian countries with robust surveillance data (Japan, South Korea and Taiwan).[2] We recently reported that KD incidence increased in Ontario, Canada over the past two decades.[3] Although KD is self-limiting, the associated vasculopathy can cause cardiovascular complications in the acute and subacute phases, particularly coronary artery aneurysms (CAA).[4] KD is the most common cause of acquired childhood heart disease in developed countries.[5,6] However, intravenous immune globulin (IVIG) treatment has significantly reduced cardiovascular morbidity.[7]

KD causes inflammation of medium-sized arteries, with a predilection for the coronary vessels. During the acute phase of KD, a necrotizing arteritis causes arterial wall destruction and aneurysm formation.[8] A subacute vasculitis then persists for months to years, disrupting the internal elastic lamina and media. Finally, luminal myofibroblastic proliferation can result in stenosis

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and thrombus formation, explaining late coronary events post-KD.[9–14] Long-term cardiovascular outcomes[12–14] following childhood KD are associated with the severity of initial coronary involvement.[4,11,15–18] Children with large CAA have high rates of myocardial infarction (MI) and mortality.[11,18,19] Recent studies of intermediate cardiovascular disease markers suggest that children with lesser coronary involvement may also be at long-term cardiovascular risk, although the role of accelerated atherosclerosis is disputed.[20–23] Autopsy specimens demonstrate coronary calcification, myointimal proliferation, and thrombosis without atherosclerosis.[8,24] However, KD survivors have more abnormal lipid profiles, obesity, decreased physical activity, higher glycosylated hemoglobin, and blood pressure than healthy comparators, which may promote atherosclerotic disease.[20,21,25–27]

Ontario's publicly funded healthcare system and linked health administrative databases provides a unique opportunity to study cardiovascular outcomes after KD diagnosis. We conducted a population-based cohort study of pediatric KD hospitalizations, to determine the risks of cardiovascular events and mortality over a 24-year period. We hypothesized that children with KD would have a higher risk of cardiovascular events and mortality within the first year following diagnosis and those with CAA would remain at higher risk throughout follow-up.

METHODS

Setting and design

We performed a population-based retrospective cohort study of children hospitalized for KD in Ontario. Ontario is Canada's largest province, containing 3 million children and a single-payer healthcare system.[28] This project was authorized under section 45 of Ontario's Personal Health Information Protection Act and approved by Hamilton Integrated Research Ethics Board. Our study was conducted and reported in accordance with STROBE[29] and RECORD[30] statements.

Study population

We identified all hospitalized children (0–18 years) with a discharge diagnosis of KD between April 1995 and March 2018 ("KD cohort"). KD was defined by International Classification of Diseases, 9th Revision (ICD-9) [446.1] or ICD-10 [M30.3] codes in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database.[31] These diagnostic codes have been validated using this database (positive predictive value 93.5%).[31] We then identified a non-exposed cohort, including all Ontario children not meeting inclusion criteria for the KD cohort. From both cohorts, we excluded individuals with a prior KD hospitalization between April 1988 and March 1995 (7-year lookback) and included only the first eligible hospitalization during our study. Non-residents of Ontario and those living in the South East Local Health Integration Network were excluded due to incomplete records. We matched each KD case with 100 non-exposed individuals based on index year, age and sex. A 1:100 matching strategy was selected a priori given the low anticipated frequency of cardiovascular events in non-exposed children.

Data sources

The study utilized Ontario provincial health administrative databases stored at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. ICES contains records for all residents with Ontario Health Insurance Plan (OHIP) coverage (>99% of the population). We utilized the following databases: CIHI Discharge Abstract Database, CIHI Same Day Surgery, National Ambulatory Care Reporting System for emergency department visits after 2003, OHIP for physician billings (diagnostic and fee codes), and the Registered Persons Database (a vital statistic registry). Descriptions of the database and administrative codes used are in Appendix 1. Datasets were deterministically linked through unique encrypted identifiers and analyzed at ICES. Study investigators had access to complete and uncleaned data for analysis.

Outcomes

The study enrollment date for the KD cohort was one day post-discharge (to exclude in-hospital events coded on the discharge date). The non-exposed cohort was randomly assigned enrollment dates based on hospitalization dates of the KD cohort. Participants were followed until death, provincial emigration, outcomes of interest, or March 2019.

Our primary outcome was Major Adverse Cardiac Events (MACE; cardiovascular death, transient ischemic attack (TIA) or stroke, and MI composite), using codes summarized in Appendix 1. MACE was selected as the primary outcome since it is commonly used in cardiovascular outcome research[32–34] and is reliably captured using ICES administrative data.[35–38] All outcomes were defined by administrative coding.

Secondary outcomes included composite cardiovascular events, defined as the following diagnostic and procedural events:

a. Diagnostic events: MI, other ischemic heart disease (IHD), TIA, stroke (hemorrhagic/infarction), peripheral vascular disease, vascular aneurysm or dissection, myocarditis/pericarditis, arrhythmias (atrial/ventricular), heart failure, non-rheumatic valvular disease, cardiomyopathy, cardiac arrest, thromboembolism.
b. Procedural events: percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), other coronary procedures, carotid artery procedures (e.g., endarterectomy), peripheral vascular procedures (e.g., bypass, dilatation, repair, endarterectomy), aneurysm procedures, implantable defibrillator or pacemaker insertion, arrythmia procedure (e.g., ablation, cardioversion), valve procedures, cardiac transplantation.

Other secondary outcomes were all-cause mortality, "ischemic" cardiovascular events (composite of MI, IHD, TIA/stroke, carotid artery procedures, peripheral vascular disease or procedures, PCI, or CABG), hypertension, and individual cardiovascular events.

Demographics, co-morbidities

Demographic variables assessed included age, sex, rural status (community size <10,000 persons), neighborhood income quintile (by postal code),[39] and ethnicity (by surname-based algorithm for Chinese and South Asian individuals).[40] Hospitalization characteristics included admission year, hospital, length of stay, PICU admission, and CAA presence. We looked back to birthdate (or April 1991 if born prior) for pre-existing co-morbidities: prior cardiovascular events (defined by composite cardiovascular event codes), congenital heart disease, juvenile idiopathic arthritis, systemic lupus erythematosus, vasculitis, chronic/end-stage kidney disease, solid organ transplant, lipid disorders, and coagulation/bleeding disorders. We looked back three years to determine the Pediatric Medical Complexity Algorithm (PMCA) classification (a validated algorithm for categorizing children by medical complexity using health administrative data).[41]

Statistical analysis and reporting

Baseline characteristics were reported using distribution-appropriate univariate tests. A p value of <0.05 was considered statistically significant. In accordance with ICES data privacy policies, cell sizes ≤5 individuals were not reported (NR). We determined the incidence of each outcome (IR; incident events per 1000 person-years (py) of study follow-up for that cohort). Time-to-event analysis was performed by Kaplan–Meier method for: (1) MACE, (2) composite cardiovascular events, and (3) all-cause mortality; compared by Gray K-sample test. We developed Cox proportional hazards models to determine the association of KD with outcomes, using the non-exposed cohort as the reference. Once a participant experienced an event, they were removed from the respective model to avoid double-counting. We estimated unadjusted hazard ratios (HR) and 95% confidence intervals (CI) throughout follow-up. Due to proportionality assumption violations, we created time-dependent Cox models for the following time periods post-discharge: 0–1 year, 1–5 years, 5–10 years, and ≥10 years. We calculated adjusted HR (aHR) using the following variables: rural status, ethnicity, neighborhood income quintile, PMCA classification, cardiovascular events, and congenital heart disease. These variables were selected a priori as potential confounders for cardiovascular events post-KD. We decided a priori to perform an exploratory subgroup analysis for cardiovascular events among KD survivors with CAA within 90 days of hospitalization (KD CAA+) and without CAA (KD CAA–). We selected 90 days post-hospitalization as a proxy for no coronary involvement during the acute/subacute illness phases, as suggested by American Heart

Association (AHA) guidelines.[4] Finally, we performed a post hoc analysis to determine the incidence of MACE and composite cardiovascular events, stratified by ethnicity.

RESULTS

Baseline characteristics

We included 4597 children surviving hospitalization for KD and 459,700 matched non-exposed children between 1995 and 2018 in Ontario (participant flow diagram, Supplementary Fig. 1). Baseline characteristics are described in Table 1. Among KD survivors, 3307 (71.9%) were aged 0–4 years at hospitalization and 2763 (60.1%) were male. Rural residence was less common among KD survivors. Most children in both cohorts did not have any chronic disease prior to enrollment. KD survivors had more prior cardiovascular events and congenital heart disease. Among KD survivors, median hospital length of stay was 3 days (IQR 2–4).

Incidence of cardiovascular events and death

Median follow-up was 11.1 years (IQR 5.5–17.0) for KD survivors and 10.0 years (IQR 4.5–16.0) for non-exposed children. Throughout follow-up, MACE occurred in 79 (1.7%) KD survivors (IR 1.5/1000py, 95% CI 1.2–1.9) vs. 3332 (0.7%) non-exposed children (IR 0.7/1000py, 95% CI 0.7–0.7) (Table 2). Composite cardiovascular events occurred in 632 (13.8%) KD survivors (IR 13.6 events/1000py, 95% CI 12.6–14.7), compared to 16,065 (3.5%) non-exposed children (IR 3.4/1000py, 95% CI 3.3–3.5). KD survivors experienced MACE (Fig. 1a) and composite cardiovascular events (Fig. 2a) sooner than non-exposed children. Among KD survivors, 38.0% of MACE ($n = 30$) and 48.3% of composite cardiovascular events ($n = 305$) occurred within the first year post-discharge. Within the first 5 years, 63.3% of MACE ($n = 50$) and 71.2% of composite cardiovascular events ($n = 450$) occurred. However, 16.5% of MACE ($n = 13$) and 16.6% of composite cardiovascular events ($n = 105$) occurred >10 years post-discharge. There were no significant differences in the incidence of MACE among KD survivors, when stratified by ethnicity (Chinese, South Asian, or Other; Supplementary Table 1).

KD survivors had a higher incidence of cardiovascular diagnoses and procedures vs. non-exposed children (Table 2 and Supplementary Table 2). The most frequent cardiovascular diagnoses among KD survivors were ischemic heart disease (231 children, 4.6/1000py), arrhythmias (229, 4.5/1000py), hypertension (159, 3.1/1000py), peripheral vascular disease (107, 2.1/1000py), TIA and stroke (61, 1.2/1000py), and congestive heart failure (49, 0.9/1000py). Acute MI occurred in 16 (0.4%) KD survivors. Twenty KD survivors underwent valve procedures. The most common procedure was percutaneous angioplasty and six of these children had pre-existing congenital heart disease. PCI or CABG occurred in twelve, defibrillator or pacemaker insertion in eight, and arrhythmia procedures in seven individuals.

All-cause mortality occurred in nine (0.2%) KD survivors (IR 0.2/1000py, 95% CI 0.1–0.3), which was less frequent than in non-exposed children (2012 (0.4%), IR 0.4/1000py, 95% CI 0.4–0.4). No cardiovascular deaths occurred. Death due to neoplastic or hematological disorders, endocrine or metabolic disorders, and accidental or intentional self-harm each occurred in ≤5 KD survivors. Non-exposed children experienced death sooner vs. KD survivors (Supplementary Fig. 2).

Risks of cardiovascular events and death

KD survivors had significantly increased risks of MACE between 0–1 and 5–10 years post-discharge (Fig. 3 and Supplementary Table 3). Their risk of MACE was also higher between 1–5 and >10 years, but this was not statistically significant after adjustment for potential confounders. KD survivors were also at significantly increased risk of composite cardiovascular events at all follow-up time periods vs. non-exposed children. For both MACE and composite cardiovascular events, the risk was greatest in the first year post-discharge.

Compared to non-exposed children, KD survivors also had increased risks of multiple individual cardiovascular outcomes (Supplementary Fig. 3 and Supplementary Table 3). KD survivors had a significantly increased risk of acute MI (aHR 2.85, 95% CI 1.67–4.87) and PCI or CABG procedure (aHR 11.02, 95% CI 5.74–21.17) throughout follow-up. KD survivors had a lower risk of

Table 1. Baseline characteristics, by Kawasaki disease status.

Variable	Kawasaki disease cohort, $N = 4597$	Non-exposed cohort, $N = 459{,}700$
Patient characteristics		
Age, 0–4 years	3307 (71.9%)	330,782 (72.0%)
Age, 5–9 years	1083 (23.6%)	108,224 (23.5%)
Age, 10–18 years	207 (4.5%)	20,694 (4.5%)
Male sex	2763 (60.1%)	276,300 (60.1%)
Rural status	279** (6.1%)	46,897 (10.3%)
Income quintile		
1 (low)	947* (20.7%)	98,908 (21.7%)
2	855* (18.7%)	88,056 (19.3%)
3	885* (19.3%)	90,252 (19.8%)
4	978* (21.3%)	93,723 (20.6%)
5 (high)	916* (20.0%)	84,587 (18.6%)
PMCA classification[a]		
Non-chronic disease	4250 (92.5%)**	441,799 (96.1%)
Non-complex chronic disease	257 (5.6%)**	12,764 (2.8%)
Complex chronic disease	90 (2.0%)**	5137 (1.1%)
Past medical history		
Any cardiovascular event	172** (3.7%)	11,236 (2.4%)
Juvenile idiopathic arthritis	NR	23 (<0.1%)
Systemic connective tissue disorder	8** (0.2%)	244 (0.1%)
Solid organ transplant	0	48 (<0.1%)
Chronic kidney disease	11 (0.2%)	660 (0.1%)
Congenital heart disease	197** (4.3%)	13,056 (2.8%)
Index admission characteristics		
Mean length of stay, in days ± SD	3.6 ± 3.1	N/A
Median length of stay, in days (IQR)	3 (2–4)	N/A
PICU admission	113 (2.5%)	N/A
Index hospital site		
Toronto (Sick Kids)	1599 (34.8%)	N/A
Ottawa (CHEO)	341 (7.4%)	N/A
McMaster (MCH)	234 (5.1%)	N/A
London (LHSC)	167 (3.6%)	N/A
Other	2256 (49.1%)	N/A

*p value < 0.05.
**p value < 0.001.
[a]Pediatric Medical Complexity Algorithm (PMCA) is a classification system for identifying children with chronic complex disease using administrative health data. We used the "least conservative version" of the PMCA.

Table 2. Incidence of cardiovascular events, by Kawasaki disease status.

Outcome*	Kawasaki disease survivors ($N = 4597$)		Non-exposed ($N = 459,700$)	
	n (%)	Incidence (/1000py)	*n* (%)	Incidence (/1000py)
Primary outcome				
MACE	79** (1.7)	1.53	3332 (0.7)	0.69
Secondary outcomes				
Composite cardiovascular events	632** (13.8)	13.6	16,065 (3.5)	3.4
MI and ischemic heart disease	247** (5.4)	4.73	3302 (0.7)	0.75
Arrhythmias (atrial and ventricular)	229** (5.0)	4.53	8263 (1.8)	1.89
Congestive heart failure	49** (1.1)	0.94	741 (0.2)	0.17
TIA and stroke	61** (1.3)	1.18	2282 (0.5)	0.52
Peripheral vascular disease	107** (2.3)	2.09	863 (0.2)	0.20
Hypertension	159** (3.5)	3.11	9383 (2.0)	2.15

*Outcomes were measured throughout median 11.1-year follow-up for Kawasaki disease survivors and 10.0-year follow-up for non-exposed children.
MACE Major Adverse Cardiac Event, *MI* myocardial infarction, *TIA* transient ischemic attack.
**p value < 0.001.

all-cause mortality vs. non-exposed children throughout follow-up (aHR 0.36, 95% CI 0.19–0.70).

Cardiovascular events, by coronary artery aneurysm status

CAA+ KD survivors had the highest incidence of MACE (15 (10.4%), IR 9.2/1000py) and composite cardiovascular events (70/144 (48.6%), IR 67.3/1000py) (Figs. 1b and 2b and Supplementary Table 4). CAA+ KD survivors were at significantly higher risk of MACE between 0 and 1 year post-discharge (aHR 13.72, 95% CI 6.74–27.93) and composite cardiovascular events at all time periods (Supplementary Fig. 4) vs. non-exposed children. Other time periods could not be reported for MACE due to low event numbers (≤5 individuals). CAA– KD survivors also had high incidence of MACE (64 (1.4%), IR 1.3/1000py) and composite cardiovascular events (676/4453 (15.2%), IR 15.2/1000py) (Supplementary Table 4). CAA– KD survivors had a significantly higher risk of MACE between 0-1 year (aHR 2.52, 95% CI 1.63–3.90) and 5–10 years post-discharge (aHR 1.93, 95% CI 1.13–3.27) and composite cardiovascular events at all time periods vs. non-exposed children.

DISCUSSION

In our study, KD survivors were at increased risk of MACE and composite cardiovascular events, compared to non-exposed children. These risks were highest in the first year post-discharge and decreased over time. KD survivors were also found to have a lower risk of death throughout follow-up.

KD survivors without CAA are considered to be low-risk for subsequent cardiac events.[11] Among 594 Japanese KD survivors in the pre-IVIG era,[11] 28 (5%) developed coronary stenosis and 11 (2%) MI. Children without CAA had no late cardiac events. In 1006 Japanese children with KD and CAA, coronary events occurred in 127 (13%) during median 6.4-year follow-up, but no events occurred in those with small CAA.[17] Among 1073 Taiwanese children with KD, 14 developed MI or death (1.6%; 13 with large CAA) during median 5.6-year follow-up.[42] In a study of 500 American KD survivors, 24 (5%) experienced MACE, all with large CAA.[15] Holve et al. matched 546 American KD cases to 2218 controls (mean 14.6-year follow-up).[16] Only five KD cases developed MI or cardiac death (multivariate HR for cardiac events: 2.29, 95% CI 0.71–7.30). Outcome data was also recently published from the International Kawasaki Disease Registry (median 2.1-year follow-up).[18] Among children with large CAA, the 10-year cumulative incidence of major adverse cardiac complications was 14% and cardiac death was 2%. In all of these studies, children with small regressed CAA appear to have similar cardiovascular outcomes to KD survivors that never develop CAA.[15,16,18,42] In comparison, we found that KD survivors without CAA were also at increased risk of MACE and composite cardiovascular events. This finding may be due to our study's larger sample size, longer follow-up, and multiple data sources. However, there may be misclassification of CAA based on the administrative coding definition used. If KD patients did not have an administrative code for CAA within 90 days of hospitalization, they were classified as CAA negative. Using administrative databases alone, we cannot verify the absence of CAA in these individuals. CAA coding could be missed if echocardiography was not performed, CAA were misdiagnosed, or underreported to administrative datasets. This may have inflated the observed incidence of cardiovascular events in the CAA– cohort. As such, the CAA subgroup analysis should be considered exploratory.

Mortality following KD is uncommon (<1%) and typically occurs from MI, aneurysm rupture, or arrhythmia.[6,11,43] Among 6576 Japanese children with KD, the standardized mortality ratio (SMR) was increased (vs. general population) during the acute phase (SMR 8.22, 95% CI 3.82–16.9)[44] and after the acute phase only for individuals with cardiac involvement (SMR 1.86, 95% CI 1.02–3.13).[43] Interestingly, children without cardiac involvement had lower mortality after the acute phase (SMR 0.65, 95% CI 0.41–0.96); due to fewer fatal injuries, poisonings, and suicide.[43] KD survivors have high reported rates of anxiety, perceived vulnerability, and lower health-related quality-of-life.[27,45,46] These findings suggest that KD survivors may engage in fewer risk-taking behaviors. In our study, we also found that all-cause mortality was less frequent in KD survivors than non-exposed children.

KD survivors are also at-risk of other cardiovascular complications.[24] Myocarditis is common during the acute phase (20–56%) and typically recovers within 2–6 months.[47,48] However, myocardial biopsies years later often demonstrate myocardial hypertrophy, fibrosis, and myocyte disarray.[49] In our study, 0.4% of KD survivors developed myocarditis/pericarditis and 1.1% developed heart failure. Arrhythmias can occur due to myocardial ischemia and fibrosis.[50] Among 60 Japanese KD survivors that experienced MI, 19% developed ventricular tachycardia during 10-year follow-up.[50] Abnormal electrocardiograms are also more common among KD survivors (10% vs. 3% of non-exposed).[51] In our study, 5% of KD survivors developed arrhythmias, eight children underwent defibrillator/pacemaker insertion, and seven children underwent arrhythmia procedures. We also found that KD survivors had higher rates of hypertension, TIA/stroke, and peripheral vascular disease diagnoses within the first five years post-discharge.

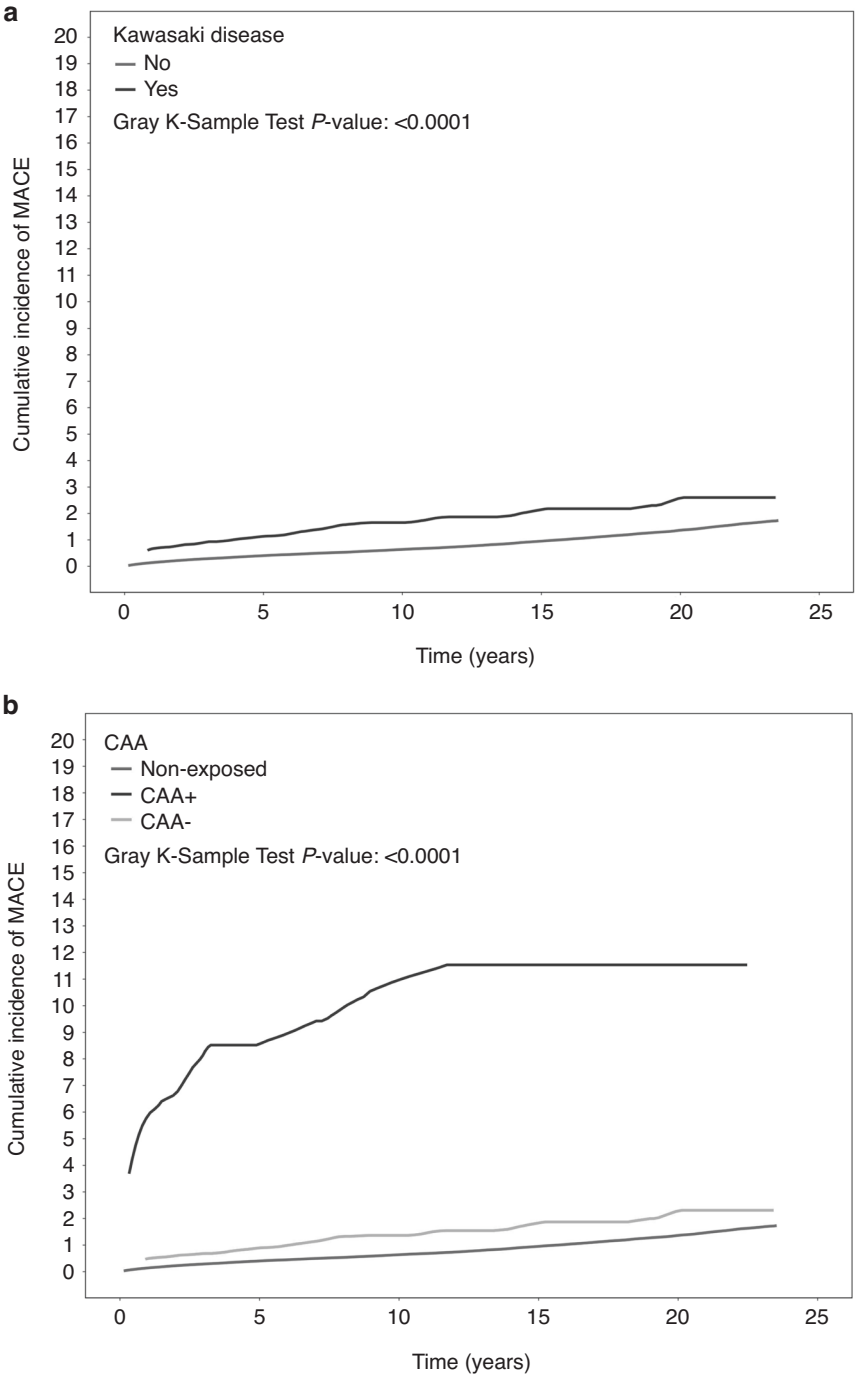

Fig. 1 Cumulative incidence of major adverse cardiac events (MACE). a Kaplan–Meier curve of major adverse cardiac events (MACE; fatal cardiovascular event, TIA or stroke and acute MI composite) among Kawasaki disease survivors (blue) vs. non-exposed children (red) post-discharge. **b** MACE among Kawasaki disease survivors with coronary artery aneurysm (CAA+, blue) vs. without (CAA–, green) vs. non-exposed children (red). Due to small cell sizes, each curve represents the moving average. The first point on each curve represents the first 100 events (for Kawasaki disease yes/no, CAA– and non-exposed cohorts) and the first 10 events (for the CAA+ cohort). The number of cumulative events and patients-at-risk are also not displayed due to small cell sizes.

Additional screening and follow-up of KD survivors may increase detection of subclinical complications. Ischemic stroke has been reported in KD patients due to occlusion of the cerebral or carotid arteries, typically in patients with CAA.[52] Furthermore, some KD patients demonstrate signs of subclinical cerebral vasculitis and hypoperfusion on brain imaging.[45,52–55] Peripheral vascular disease may be attributable to systemic arterial aneurysms.[56] Other studies have also found evidence of abnormal vascular endothelial function and intermediate markers for atherosclerosis among KD survivors, which may increase the risk of hypertension and long-term atherosclerotic diseases.[20,22,57–59]

Our study has multiple strengths. To our knowledge, this is the largest cardiovascular outcomes study of North American KD survivors, with median 11-year follow-up data. Most prior studies report shorter follow-up periods (<10-year) and focus on children with CAA, which represent <5% of modern cases.[31] Many studies

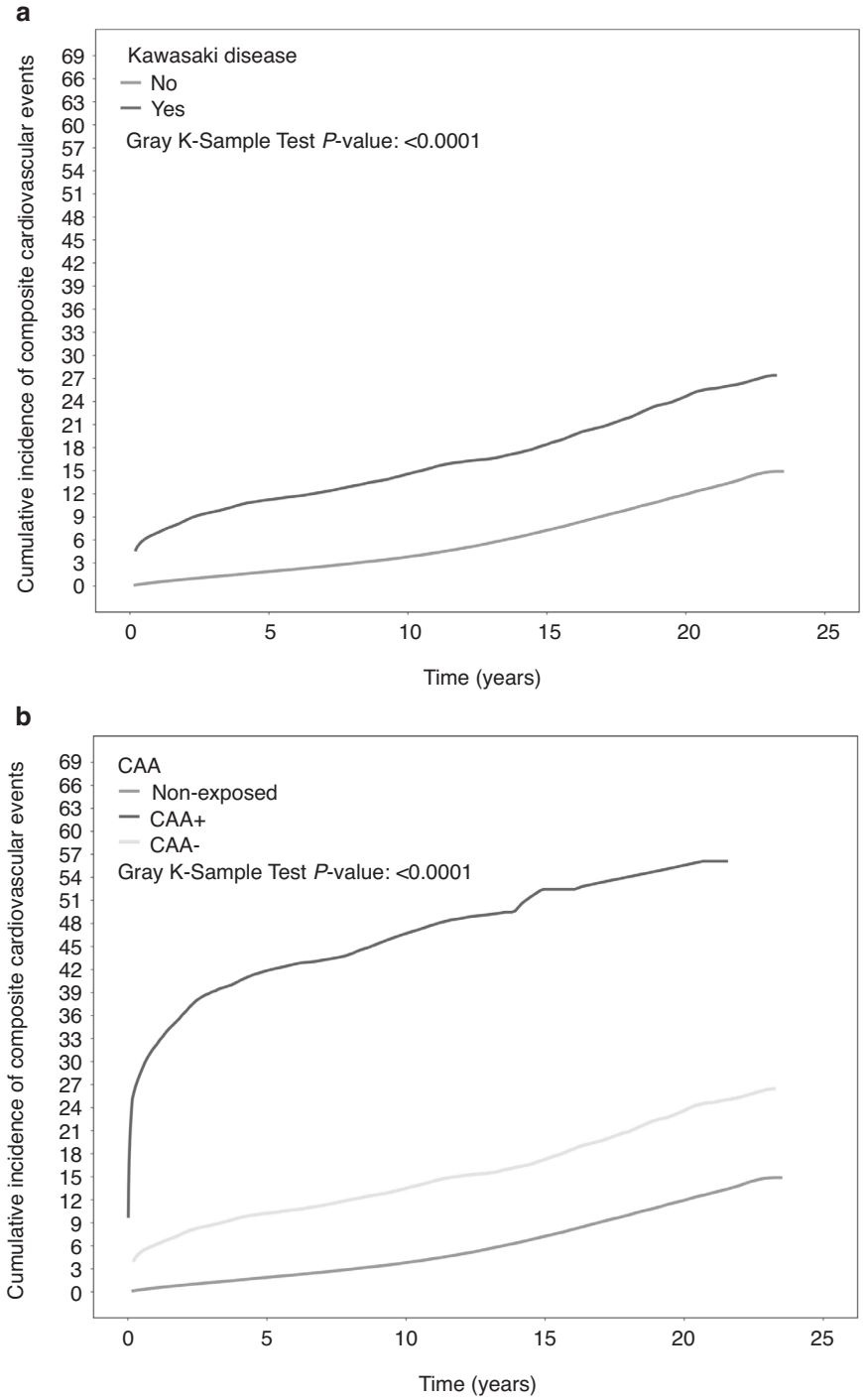

Fig. 2 Cumulative incidence of composite cardiovascular events. a Kaplan–Meier curve of composite cardiovascular events among Kawasaki disease survivors (blue) vs. non-exposed children (red) post-discharge. **b** Composite cardiovascular events among Kawasaki disease survivors with coronary artery aneurysm (CAA+, blue) vs. without (CAA–, green) vs. non-exposed children (red). Due to small cell sizes, each curve represents the moving average. The first point on each curve represents the first 100 events (for Kawasaki disease yes/no, CAA– and non-exposed cohorts) and the first 10 events (for the CAA+ cohort). The number of cumulative events and patients-at-risk are also not displayed due to small cell sizes.

were also performed in the pre-IVIG era, when cardiovascular morbidity was more common. IVIG was widely available throughout our study period, increasing our study's generalizability. Using a matched non-exposed cohort allowed us to estimate cardiovascular event and mortality risks attributable to KD diagnosis. Linked administrative databases within a publicly funded healthcare system provided multiple data sources. Loss to follow-up was minimal, occurring only due to provincial emigration (3.3% KD cases vs. 9.8% non-exposed, throughout follow-up).

Health administrative database research does have limitations. Discharge codes for KD have a high reported positive predictive value.[60,61] They have been validated using the Ontario Discharge Abstract Database with concurrent surveillance survey data.[31] However, our characterization of KD is limited. We cannot

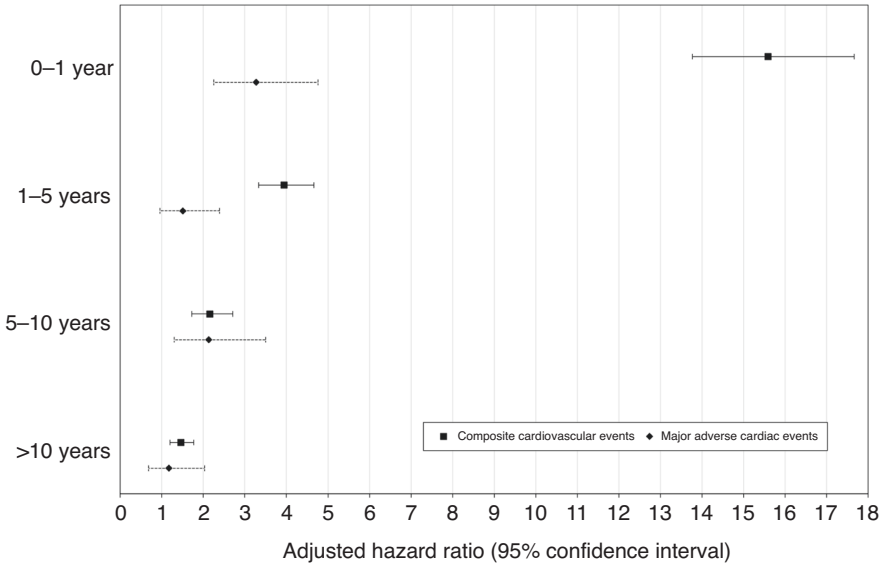

Fig. 3 Time-stratified hazard ratios for major adverse cardiac events and composite cardiovascular events, among Kawasaki disease survivors vs. non-exposed children. *Adjusted for: rural status, ethnicity, income quintile, PMCA classification, prior cardiovascular event or congenital heart disease. Major adverse cardiac events (MACE): cardiovascular death, TIA or stroke, and acute MI composite. Forest diagram of the adjusted hazard ratios for major adverse cardiac events (MACE; diamond, dashed line) and composite cardiovascular events (square, solid line), comparing Kawasaki disease survivors vs. non-exposed children (reference group).

distinguish complete from incomplete KD, determine symptom duration pre-hospitalization, or identify missed cases. We cannot evaluate IVIG or other medication administration, due to incomplete medication data. Administrative coding for CAA has not been validated, which introduces potential misclassification bias. However, these diagnostic codes were specific to CAA and our CAA frequency was consistent with other studies.[7,16] We could not determine CAA size or regression patterns using administrative data. This prevented us from risk stratifying KD survivors, as outlined in the AHA guidelines.[4] This is a significant limitation, since adverse cardiovascular outcomes are strongly correlated with the severity of CAA involvement, and therefore occur predominantly in a small proportion of high-risk KD survivors. We used validated coding algorithms to define most cardiovascular outcomes. Administrative coding for certain diagnostic outcomes (i.e., myocarditis/pericarditis, cardiac arrest, vascular aneurysm, cardiomyopathy, and non-rheumatic valvular disease) have not been validated. Although validation studies do not exist for procedural codes, accurate procedural coding is required for physician/facility reimbursement in Ontario. Differences in healthcare utilization between KD and non-exposed children may create ascertainment bias. However, given that most cardiovascular outcomes studied would require hospitalization, incidental diagnoses may be uncommon. One exception was hypertension, where additional blood pressure screening of KD survivors may increase detection. We therefore excluded hypertension from our composite cardiovascular event outcome.

CONCLUSIONS

KD survivors were at increased risk of cardiovascular events but lower risk of death, compared to non-exposed children. KD survivors with CAA had the highest risk of cardiovascular events. This justifies cardiovascular disease surveillance and risk reduction among high-risk KD survivors (i.e., patients with CAA). Future research should evaluate risk factors for late cardiovascular events among KD survivors, with the goal of creating risk stratification tools to identify individuals that would benefit from additional surveillance.

DATA AVAILABILITY

Deidentified individual participant data will not be made available.

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AUTHOR CONTRIBUTIONS

C.R., R.C. and M.B. conceptualized and designed the study, coordinated and supervised data collection and analysis, drafted the initial manuscript, and reviewed and revised the manuscript. H.S. and E.D. conceptualized and designed the study, coordinated and supervised data collection and analysis, and reviewed and revised the manuscript. S.B., C.D., T.M. and R.P. reviewed and revised the proposed study design, reviewed data analyses, assisted with data interpretation, and reviewed and revised the manuscript. A.G. conceptualized and designed the study, was primarily responsible for data collection and analysis, and reviewed and revised the

manuscript. All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

This project was authorized under section 45 of Ontario's Personal Health Information Protection Act and was approved by Hamilton Integrated Research Ethics Board.

ADDITIONAL INFORMATION

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