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POPULATION STUDY ARTICLE

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Evaluating the time-varying risk of hypertension, cardiac events, and mortality following Kawasaki disease diagnosis

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BACKGROUND: This study evaluated the risk of hypertension, major adverse cardiac events (MACE), and all-cause mortality in Kawasaki disease (KD) patients up to young adulthood.
METHODS: An inception cohort of 1169 KD patients between 1991 and 2008 from a tertiary-level hospital in Ontario, Canada was linked with health administrative data to ascertain outcomes up to 28 years of follow-up. Their risk was compared with 11,690 matched population comparators. The primary outcome was hypertension and secondary outcomes were MACE and death.
RESULTS: After a median follow-up of 20 years [IQR: 8.3], the cumulative incidence of hypertension and MACE in the KD group was 3.8% (95% CI: 2.5–5.5) and 1.2% (95% CI: 0.6–2.4%), respectively. The overall survival probability in the KD group was 98.6% (95% CI: 97.2–99.3%). Relative to comparators, KD patients were at an increased risk for hypertension [aHR: 2.2 (95% CI: 1.5–3.4)], death [aHR: 2.5 (95% CI: 1.3–5.0)], and MACE [aHR: 10.7 (95% CI: 6.4–17.9)]. For hypertension and MACE, the aHR was the highest following diagnosis and then the excess risk diminished after 16 and 13 years of follow-up, respectively. MACE occurred largely in KD patients with coronary aneurysms [cumulative incidence: 12.8%].
CONCLUSIONS: KD patients demonstrated a reassuring cardiac prognosis up to young adulthood with low events and excellent survival. KD patients were at increased risk for hypertension, but this excess risk occurred early and declined with time.

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IMPACT:

- With the current standard of care, KD patients demonstrated favorable cardiac prognosis, with low events of hypertension, MACE, and excellent survival.
- Hypertension and MACE risk appear to be highest around the time of KD diagnosis.
- MACE occurred primarily in KD patients with coronary aneurysms.
- Our findings are reassuring to KD patients, families, and their providers.
- Our study demonstrated an association between KD exposure and hypertension. This association is relatively novel. Previous studies have remained conflicting if KD contributes to long-term atherosclerotic risk.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis that primarily occurs in children, and is the leading cause of acquired heart disease in childhood in developed countries.[1] Without treatment, approximately 25% of children can develop coronary artery aneurysms (CAA).[2,3] Complications related to CAA can include rupture, myocardial ischemia, and sudden death.[4–6] Therefore, KD has the potential to cause severe cardiac complications during childhood and beyond.

While speculated, the long-term cardiac prognosis of all KD children, particularly those with normal coronary arteries, remains unclear. Current long-term prognosis studies have reported greater than 90% survival and a major adverse cardiac event (MACE)-free survival ranging from 36 to 96% at 30 years.[6–11] However, these results are not generalizable to the majority of children with KD, as these studies frequently exclude children with normal coronary arteries. Eliminating these patients (i.e., those without CAA) results in a limited understanding of the prognosis of the entire KD population, especially considering intravenous immunoglobulin (IVIG) therapy has significantly reduced the incidence of CAA.[1,12–14]

Furthermore, it remains unclear if patients with KD demonstrate ongoing low states of vascular inflammation and/or dysfunction, which may predispose them to earlier or accelerated atherosclerotic disease. Studies have been conflicting; some studies have reported persistent vascular abnormalities including increased arterial wall thickness and stiffness in KD patients when compared to those without a previous history of KD,[15–19] while other studies reported no differences in these measures.[20–22] It remains unknown if these abnormal sonographic findings translate to more clinical diseases later in life, such as higher rates of hypertension, stroke, or myocardial infarctions.

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Therefore, the objective of this study was to evaluate whether individuals with KD were at an increased risk for hypertension, all-cause mortality, and MACE over time, when compared to individuals without KD. We hypothesized that individuals with KD were at higher risk for hypertension, MACE, and death relative to those without KD.

METHODS

Study design and setting

This was a retrospective closed-inception data linkage study. Patients with KD from a tertiary hospital (The Hospital for Sick Children – SickKids) in Ontario, Canada were linked to health administrative data at ICES (www.ices.on.ca), and then compared with population comparators, in order to ascertain outcomes (Supplementary Fig. 1). Ontario has a single-payer Ontario Health Insurance Plan (OHIP) in which most physician and hospital services are covered. Institutional ethics approval was obtained from SickKids, Toronto, Canada.

Data sources

The SickKids KD cohort was used to identify and describe KD patients. This cohort includes all children diagnosed with KD at SickKids. Collected information included clinical features, treatments, and echocardiogram findings.

The Registered Persons Database (RPDB) includes demographic information of all current and former residents of Ontario and was used to identify comparators. Postal code of residence, when linked to the Canadian Census, was used to derive the neighborhood income quintile data. Rurality was also determined by the RPDB, defined as individuals residing in a community size ≤10,000 residents. All-cause mortality was determined with the RPBD. The registration of deaths within RPDB is virtually complete due to legal requirements.[23]

To identify and match individuals on ethnicity, the ICES-derived ETHNIC database was used, which includes encoded classifiers for either South Asian, Chinese, or other on the basis of surnames (surnames are not included in the database). Validation studies against self-identified ethnicity indicate specificities of 99.7 and 99.7% and sensitivities of 50.4 and 80.2% for South Asians and Chinese Canadians, respectively.[24]

The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), Same Day Surgery (SDS) database, and the OHIP claims database were used to identify hypertension and MACE. CIHI-DAD and SDS include information from hospital or day surgery records, including hospitalization dates, associated diagnoses, and procedures. The OHIP claims database identifies physician services and includes the date of encounters and associated diagnosis code. The OHIP Claims database uses an adaptation of the International Classification of Diseases (ICD)-8 coding system, and the CIHI-DAD/SDS uses the ICD-9 and ICD-10 system (ICD-10 was used from 2002 onwards).[25] Procedures were coded with either the Canadian Classification of Procedures (CCP) or Canadian Classification of Interventions (CCI) systems (CCI was used from 2002 onwards).

Study population

The KD group included patients diagnosed with KD as children (<18 years old) at SickKids from January 1, 1991, until December 31, 2008. The index date was defined as the date of KD diagnosis. We excluded individuals who had missing/invalid health card numbers and could not be linked to health administrative databases.

The general population comparator (non-KD) group included Ontario residents without a diagnosis of KD (ICD-9: 446.1, ICD-10: M30.3) or a hospitalization related to the fever of unknown origin (ICD-9: 672.0, ICD-10: R50.9). The index date for comparators was defined as the index date of the matched KD patient. Ten comparators were matched with each KD patient according to sex, age, ethnicity (Chinese, South Asian, or Other), regional area of residence, and within the same calendar year.

For both groups, we excluded individuals with a previous diagnosis of hypertension, congestive heart failure (CHF), ischemic heart disease (IHD), stroke, or cardiac interventions (determined from administrative data) within 2 years prior to the index date.

Outcomes

The primary outcome, hypertension, was defined as one hospitalization with a hypertension diagnosis (ICD-9 codes: 401.x–405.x, or ICD-10 codes: I10.x–I13.x, I15.x), or at least two physician billing claims related to hypertension within a 2-year period. The date of hypertension was defined as the date of the first hypertension record. This case definition has been previously validated in patients ≥35 years old (specificity: 95%, sensitivity: 72%, positive predictive value: 87%).[26]

Secondary outcomes included all-cause mortality (defined as the date of death on RPDB) and MACE. MACE was a composite outcome that included validated case definitions of IHD, stroke, cardiac interventions, and CHF[27–31] (Supplementary Table 1).

Statistical analysis

The reporting was in compliance with the Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) statement.[32] We conducted descriptive analyses to summarize the cohort and standardized differences were calculated to compare characteristics between KD and non-KD groups. A standardized difference >0.10 was statistically significant. Incidence rates for hypertension, MACE, and death [per 1000 person-years (PY)] were calculated by determining the number of events in each group and the overall duration (PY) of follow-up. Incidence rate ratios (IRR) were derived using Poisson regression. The absolute risk increase (ARI) was the difference in incidence rates between groups.

Survival time was the length of time from the index date to the date of the primary/secondary outcome or censoring (date of outmigration or death). Patients without a documented date of death or outmigration were right censored at the study end date. For hypertension and MACE, the cumulative incidence was evaluated and compared with Gray's test. Survival probabilities were derived with Kaplan–Meier curves and compared with the Log-Rank test. As a subgroup analysis, we evaluated the cumulative incidence of hypertension in KD patients with normal coronary arteries relative to their comparators. In addition, for each outcome, we evaluated the cumulative incidence/survival probability in the entire KD group according to the presence/absence of CAA.

Multivariable cause-specific models were performed to determine if KD exposure resulted in a difference in time to hypertension or MACE, while adjusting for income and rurality (as indicators of access to care, a potential confounder). A multivariable Cox model was used to evaluate survival. If the proportional hazards assumption was violated, we performed an expanded Cox model that included the time-dependent interaction between KD status and time.

All statistical analyses were performed using SAS Enterprise (SAS Institute Inc., Cary, NC, 2017, Version 7.15).[33] Analyses yielding a cell count of ≤5 subjects were suppressed in accordance with ICES' privacy policies. Statistical significance was defined as a two-sided p value <0.05.

Sensitivity analysis

Sensitivity analyses were performed for analyses relevant to hypertension. In order to evaluate for surveillance bias, we varied the adjusted hazard ratio (aHR) for hypertension by a range of values that reflects the degree of detection bias (bias factor). We ranged the bias factor from 0.6 to 2.0, with >1 reflecting a higher probability of hypertension detection in the KD group compared to the non-KD group.

In order to ensure that the hypertension events that were captured were not due to transient hypertension diagnoses at the time of KD hospitalization (because hypertension can occur with IVIG or steroid treatments), we conducted a landmark analysis where the index date was revised to 12 months after the initial index date.

RESULTS

Cohort

Based on eligibility, 1169 and 11,690 individuals were included in the KD group and non-KD group, respectively (Supplementary Figs. 2 and 3). Due to matching, most baseline characteristics were comparable across groups (Table 1). The median follow-up duration was 20 years (IQR: 8.3).

The clinical characteristics of the KD group are provided in Table 2. The majority of KD patients exhibited the complete subtype (839, 71.8%) and received IVIG (985, 91.7%). Overall, 781 KD patients (66.8%) had normal coronary arteries, 54 (4.6%) had coronary dilatations, 110 (9.4%) had small CAA, 27 (2.3%) had medium CAA, and 20 (1.7%) had giant CAA. The remaining 117 patients (15.4%) had missing echocardiogram information.

Table 1. Baseline demographic characteristics of KD and non-KD individuals.

Characteristic	KD group ($n = 1169$)	Non-KD group ($n = 11,690$)	SD
Age in years, median(IQR)	2 (4.0)	2 (4.0)	[b]
Age category, *n* (%)			[b]
<6 months	43 (3.7)	430 (3.7)	
≥6 months to <1 year	104 (8.9)	1040 (8.9)	
≥1 year to <5 years	716 (61.2)	7160 (61.2)	
≥5 years to <10 years	256 (21.9)	2560 (21.9)	
≥10 years to <18 years	50 (4.3)	500 (4.3)	
Year at the time of cohort entry, *n* (%)			[b]
1991–1996	362 (31.0)	3620 (31.0)	
1997–2002	445 (38.1)	4450 (38.1)	
2003–2008	362 (31.0)	3620 (31.0)	
Sex, *n* (%)			[b]
Male	730 (62.4)	7300 (62.4)	
Ethnicity, *n* (%)			[b]
Chinese	155 (13.3)	1550 (13.3)	
South Asian	31 (2.7)	310 (2.7)	
Other[a]	983 (84.1)	9830 (84.1)	
Income quintile, *n* (%)			
Q1 (lowest)	302 (25.8)	3108 (26.6)	0.02
Q2	206 (17.6)	2274 (19.5)	0.05
Q3	206 (17.6)	2139 (18.3)	0.02
Q4	246 (21.0)	2114 (18.1)	0.07
Q5 (highest)	200 (17.1)	1992 (17.0)	0.00
Rural residence			
Yes	28 (2.4)	394 (3.4)	0.06

KD Kawasaki disease, *SD* standardized difference, *IQR* interquartile range.
[a]Refers to individuals who have surnames that are not of Chinese or South Asian descent.
[b]Matching variables.

Hypertension

After 21,792 and 218,578 PY of follow-up in the KD group and non-KD group, respectively, the incidence rate of hypertension in the KD group [IR: 1.4/1000 PY (95% CI: 0.9–2.0)] was statistically significantly higher than in the non-KD group [IR: 0.6/1000 PY (95% CI: 0.5–0.7)] with an IRR of 2.2 (95% CI: 1.5–3.3, $p < 0.0001$) (Table 3). The ARI for hypertension was 0.8/1000 PY (95% CI: 0.4–1.2).

The cumulative incidence of hypertension at 10-, 20-, and 28-year follow-up in the KD group was 0.9, 2.7, and 3.8%, respectively, compared with 0.2, 1.0, and 2.5%, respectively, in the non-KD group (Fig. 1a). This comparative difference was statistically different (Gray's test *p* value <0.0001). Within the KD group, there was no statistically significant difference in the cumulative incidence according to CAA status (Supplementary Fig. 4). KD patients with normal coronary arteries continued to demonstrate an increased risk for hypertension relative to their comparators (Supplementary Fig. 5). In our landmark sensitivity analysis, the KD group continued to experience more hypertension events than the non-KD group, and this was statistically significant (Supplementary Fig. 6).

Overall, the KD group demonstrated a two-times higher relative hazard for hypertension [aHR: 2.3 (95% CI: 1.5–3.4), $p < 0.0001$] (Table 4A). With the proportional hazard assumption violated, the aHR was evaluated over follow-up time. The aHR was highest at the time of diagnosis [aHR: 8.3 (95% CI: 3.5–19.8)] and then diminished over time (Table 4B). The excess risk was observed for 16 years (Fig. 2).

Our sensitivity analysis demonstrated that a 53% higher outcome detection probability in the KD group compared to the non-KD group could explain the observed association of hypertension in KD (Supplementary Fig. 7).

Major adverse cardiac events (MACE)

The incidence rate of MACE in the KD group was 1.30/1000 PY (95% CI: 0.86–1.87) and in the non-KD group was 0.12/1000 PY (95% CI: 0.08–0.18) (Table 3). The ARI for MACE was 1.18/1000 PY (95% CI: 0.78–1.69).

The cumulative incidence of MACE at 20 and 28 years of follow-up in the KD group was 0.7 and 1.2% compared with 0.2 and 0.3% in the non-KD group (Fig. 1b). This difference was statistically significant (Gray's test *p* value <0.0001). MACE events within the KD group were largely driven by cardiac interventions (25/28 patients with MACE experienced cardiac interventions). The cumulative incidence of MACE was higher in patients with CAA compared to those without CAA (Supplementary Fig. 8).

Overall, KD exposure resulted in a 10-time increased hazard risk [aHR: 10.7 (95% CI: 6.4–17.9), $p < 0.0001$] for MACE (Table 4A). In the expanded Cox model, the initial aHR for MACE was 28.4 (95% CI: 13.0–61.8, $p < 0.0001$) and then decreased with time (Table 4B). The excess risk was observed for 13 years (Supplementary Fig. 9).

All-cause mortality

The incidence rate of mortality in the KD group was 0.45/1000 PY (95% CI: 0.45–0.83), compared to 0.19/1000 PY (95% CI: 0.14–0.26) in the non-KD group (Table 3). The ARI remained low [ARI: 0.3/1000 PY (95% CI: 0.1–0.6)].

While survival probabilities were excellent in both groups [KD group: 98.6% (95% CI: 97.2–99.3), non-KD group: 99.2% (95% CI: 98.9–99.5)], the KD group demonstrated a lower survival (log-rank test $p = 0.01$; Fig. 1c). KD exposure resulted in a 2.5-time increase in the hazard for death [aHR: 2.5 (95% CI: 1.3–5.0), $p < 0.009$], after adjusting for income quintile and rurality (Table 4A). There was no statistically significant difference in survival according to CAA status (Supplementary Fig. 10).

DISCUSSION

This study examined the long-term prognosis amongst patients with a confirmed diagnosis of KD from a large tertiary hospital in Canada. This study demonstrated a very reassuring prognosis with low event rates for hypertension and MACE, as well as excellent survival. Relative to comparators, KD patients appeared to have an increased risk for hypertension and MACE, but the excess risk occurred early after the diagnosis and diminished over follow-up time. MACE events were largely driven by cardiac interventions in KD patients with CAA.

In our study, KD patients, including those with normal coronary arteries, were at an increased risk for hypertension relative to comparators. Only a limited number of studies previously explored this association, of which only one study, to our knowledge, demonstrated a higher incidence of hypertension in KD patients.[34–38] The explanation for this increased risk remains unclear, but may be due to several mechanisms including functional or structural damage of the affected vessels,[2,39–41] inherent differences (genetic or behavioral) in the traditional risk factors for hypertension,[42–47] or ongoing low-grade systemic inflammation.[15] More studies are required to evaluate this association. Regardless, in our study, the clinical relevance of this increased relative risk is

Table 2. Clinical characteristics relevant to the KD group.

Characteristic	KD group ($n = 1169$)
Median duration of symptoms from onset to diagnosis, days (IQR)	6 (3.0)
Median length of hospitalization, days (IQR)	4 (2.0)
Median total days of fever (IQR)	6 (3.0)
KD type	
Complete KD subtype	839 (71.8)
Incomplete KD subtype	262 (22.4)
KD features per patient, *n* (%)	
≤2	55 (4.7)
3	196 (16.8)
4	450 (38.5)
5	382 (32.7)
Treatments related to KD	
Receipt of IVIG, *n* (%)	
Yes	985 (91.7)
No	89 (8.3)
Response to first IVIG, *n* (%)	
Complete response	832 (71.2)
Partial NR	72 (6.2)
Complete NR	75 (6.4)
Number of IVIG doses	
1	916 (78.4)
≥2	66 (5.6)
Receipt of corticosteroids, *n* (%)	
Yes	45 (4.1)
No	1056 (95.9)
Acute complications related to KD	
ICU stay, *n* (%)	
Yes	16 (1.4)
No	813 (69.5)
KD shock syndrome, *n* (%)	
Yes	8 (0.7)
No	464 (39.7)
Median maximum CAA *Z*-score at diagnosis, median (IQR)	0.8 (1.3)
CAA status, *n* (%)[a]	
No involvement (<2)	781 (66.8)
Dilatation (2–<2.5)	54 (4.6)
Small (≥2.5–<5)	110 (9.4)
Medium (≥5–<10)	27 (2.3)
Giant (≥10)	20 (1.7)

KD Kawasaki disease, *IVIG* intravenous immunoglobulin, *CAA* coronary artery aneurysm, *ICU* intensive care unit, *IQR* interquartile range, *SD* standardized difference, *NR* non-response.
[a]Classification determined by maximum *z*-score reported in any coronary artery.

questioned once absolute measures are taken into consideration. We determined that for every 1250 PY, the KD group had one additional case of hypertension, which we interpreted as a low-risk increase.

KD patients were also at higher risk for MACE, but the majority of these events were driven by cardiac interventions in KD patients with known CAA. Few studies have reported on the cumulative

Table 3. Incidence rates per 1000 PY of primary and secondary outcomes by presence or absence of KD exposure.

Outcome	KD group ($n = 1169$)			Non-KD group ($n = 11{,}690$)			IRR (95% CI)	ARI[b] (95% CI)
	Number of events, *n* (%)	FU time (PY)	Incidence rate[a] (95% CI)	Number of events, *n* (%)	FU time (PY)	Incidence rate[a] (95% CI)		
Hypertension	30 (2.57)	21,792	1.38 (0.93–1.97)	136 (1.16)	218,578	0.62 (0.52–0.74)	2.21 (1.49–3.28)	0.76 (0.41–1.23)
All-cause mortality	10 (0.86)	22,083	0.45 (0.22–0.83)	42 (0.36)	219,393	0.19 (0.14–0.26)	2.37 (1.19–4.71)	0.26 (0.08–0.57)
MACE	28 (2.40)	21,604	1.30 (0.86–1.87)	27 (0.23)	219,103	0.12 (0.08–0.18)	10.52 (6.20–17.84)	1.18 (0.78–1.69)

KD Kawasaki disease, *FU* follow-up, *IRR* incidence rate ratio, *ARI* absolute risk increase, *MACE* major adverse cardiac events.
[a]Rate is per 1000 PY.
[b]Absolute risk increase is per 1000 PY.

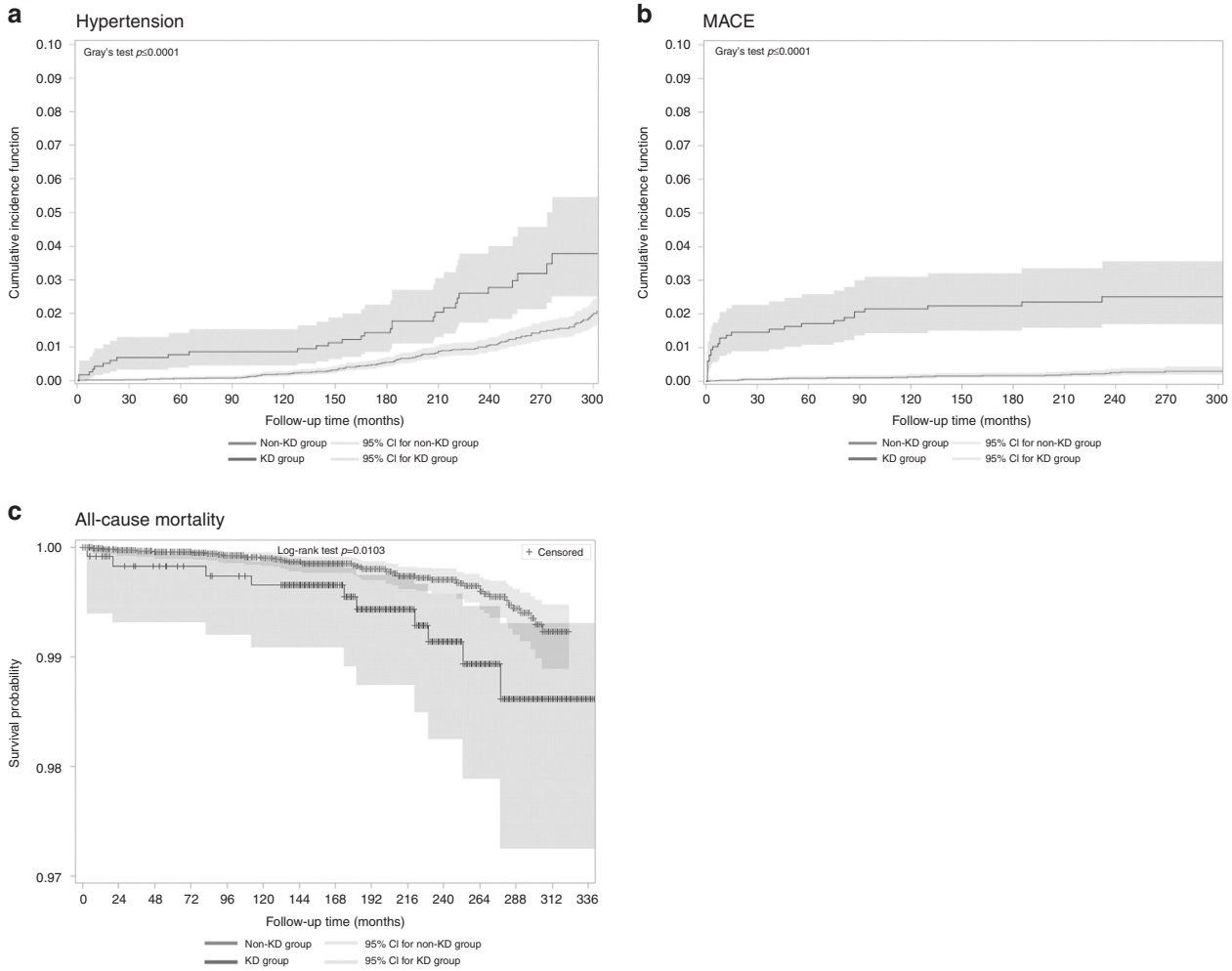

Fig. 1 Cumulative incidence/survival probability estimates of hypertension, major adverse cardiac events (MACE), and all-cause mortality. a Cumulative incidence function of hypertension. **b** Cumulative incidence function of MACE. **c** Survival probabilities of all-cause mortality. KD Kawasaki disease, CI confidence interval.

incidence of MACE, for comparison. Previous studies have reported MACE-free survival estimates between 25 and 68% at 25 years of follow-up.[6–8,10] Given that we had to adjust for the competing risk of death, we could not derive survival probabilities. In general, it appeared that MACE occurrences were lower in our study. This is likely attributed to previous studies only including KD patients with CAA, while a large proportion of our population had normal coronary arteries.

It may be possible that our results for both hypertension and MACE, but particularly for hypertension, may be influenced by surveillance bias. Surveillance bias occurs when patients in one group have a higher probability of ascertaining an outcome due to increased monitoring or testing. Given that hypertension is largely asymptomatic, it is possible that frequent surveillance after KD diagnosis can increase opportunities to pick up blood pressure abnormalities. Our sensitivity analysis demonstrated that hypertension would need to be recognized at least 1.5 times more frequently in the KD group to explain the observed increase in hypertension risk.

The overall survival of our KD patients into early adulthood was excellent. This is an improved survival estimate in contrast to the majority of published studies on mortality in the KD population. Studies that have explored survival over follow-up time in KD patients (mostly in those with CAA) have ranged from 63 to 98% beyond 20 years.[6–8,10,11]

We demonstrated that KD patients continued to demonstrate a relative increased risk for death, which contrasts with the conclusions generated from a longitudinal cohort of 6576 Japanese children.[48–52] Results from the Japanese cohort reported similar mortality rates in the KD population compared to the general population after 27 years of follow-up. This difference in conclusions may be related to the statistical methods or the genetic/ethnic composition of the two study populations. Card et al. demonstrated that indirect standardization with national population death statistics can underestimate mortality risk.[53] Furthermore, the Japanese cohort comprised only individuals of Japanese nationality while our cohort was multiethnic. Studies have previously demonstrated differences in treatment responses and CAA outcomes according to ethnicity.[54–58]

We utilized the strengths of a large cohort with rich clinical data and a universal healthcare system that captures data on Ontario residents. Linkage with administrative data offered us several advantages. First, we were able to identify patients with a confirmed diagnosis of KD, minimizing exposure misclassification. Second, we were able to explore the impact of CAA status on outcomes. Third, we were able to evaluate cardiac surveillance for KD patients up to early adulthood. Considering that the majority of KD patients do not experience active surveillance for this length of duration, the use of health administrative data to identify outcomes was critical.

Table 4. Adjusted hazard ratios (aHR) for hypertension, MACE, and all-cause mortality when comparing the KD group to the non-KD group.

Variable	Primary outcome		Secondary outcomes			
	Hypertension		MACE		All-cause mortality[a]	
	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value
A. Original model						
KD[b]	2.29 (1.53–3.44)	**<0.0001**	10.74 (6.43–17.93)	**<0.0001**	17.07 (9.14–31.89)	**<0.0001**
Income quintile						
1	Ref.	–	Ref.	0.61	Ref.	–
2	0.86 (0.54–1.39)	0.54	1.21 (0.58–2.55)	0.35	2.14 (0.82–5.61)	0.12
3	1.06 (0.68–1.64)	0.81	1.43 (0.68–3.04)	0.93	2.88 (1.07–7.76)	**0.04**
4	1.10 (0.69–1.75)	0.68	0.96 (0.43–2.15)	0.23	1.98 (0.70–5.56)	0.20
5	0.93 (0.58–1.50)	0.76	0.54 (0.20–1.46)	0.29	1.00 (0.29–3.51)	0.97
Rural[c]	2.69 (1.72–4.20)	**<0.0001**	1.84 (0.60–5.66)	0.29	1.67 (0.42–6.62)	0.46
B. Expanded model, incorporating interaction term of KD exposure with time[d]						
KD	8.31 (3.48–19.81)	**<0.0001**	28.38 (13.04–61.76)	**<0.0001**		
KD * time	0.99 (0.99–1.00)	**0.004**	0.99 (0.98–1.00)	**0.003**		
Income quintile						
1	Ref.	–	Ref.	–		
2	0.86 (0.54–1.38)	0.54	1.21 (0.58–2.53)	0.62		
3	1.06 (0.67–1.67)	0.80	1.44 (0.68–3.05)	0.34		
4	1.10 (0.70–1.72)	0.68	0.96 (0.43–2.15)	0.93		
5	0.92 (0.57–1.49)	0.75	0.54 (0.20–1.46)	0.22		
Rural	2.66 (1.65–4.31)	**<0.0001**	1.81 (0.59–5.55)	0.30		

Bold values indicate statistical significance $p < 0.05$.
MACE major adverse cardiac events, *KD* Kawasaki disease, *aHR* adjusted hazard ratio, *CI* confidence interval, *Ref.* reference group.
[a]All-cause mortality was evaluated through a Cox proportional hazards regression model, hypertension and MACE were evaluated with a cause-specific hazard regression model.
[b]Reference group is non-KD.
[c]Reference group is non-rural.
[d]Hypertension and MACE statistical models violated the proportional hazards assumption but the all-cause mortality model did not. Thus, the expanded model was only performed for hypertension and MACE.

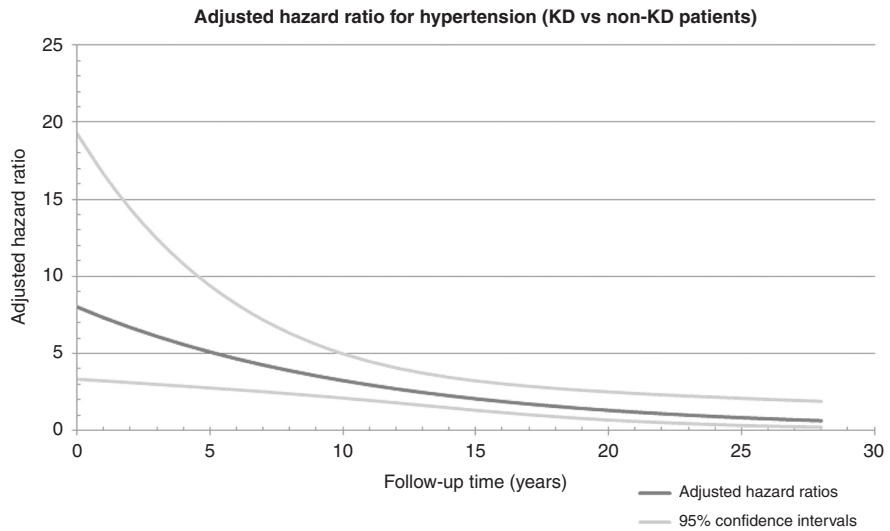

Fig. 2 Adjusted hazard ratio for hypertension (KD vs non-KD group) over follow-up time. Upper gray line reflects upper 95% CI and the lower gray line reflects the lower 95% CI. KD Kawasaki disease.

In addition to surveillance bias, our conclusions must be considered in light of additional limitations. First, the measurement of some of our covariates was imperfect that may result in residual confounding. For instance, while our study adjusted for ethnicity with a validated surnames algorithm, the algorithm only specified Chinese and South Asian surnames and was not inclusive of other East Asian surnames. As such, it is possible that the prevalence of East Asian patients in the KD

group remained underestimated. If East Asian patients are at lower risk of hypertension due to their ethnicity,[59] this may then bias our results towards the null. Second, while this study utilized validated case definitions in order to improve the accuracy of identifying outcomes, our study is still prone to outcome misclassification, resulting in imprecision. Furthermore, we had limited clinical characterization of our outcomes, such as whether there were clinical symptoms attributed to hypertension, any associated/relevant risk factors, and treatments used.

Third, while we ensured that both KD patients and population comparators did not have any preceding cardiac disease within the 2 years prior to the index date, it may be possible that individuals who were much older at the index date may have had a remote history of cardiac disease (such as congenital heart disease) that could alter their future cardiac risk. If the proportion of missed congenital heart disease occurred significantly more in the KD group compared to the non-KD group, then this may potentially falsely attribute increased cardiac risk with KD exposure. However, given that the median age at the index date was 2 years old, we do not expect this concern to significantly impact our overall findings or conclusions. Furthermore, we do not expect KD patients to be at a higher risk for congenital heart disease relative to their comparators. Finally, the results of our study may not be generalizable to all Canadians with KD. Our KD patients were selected from the largest pediatric hospital in the largest city in Canada. Thus, it may be possible that our KD population may not be representative of the patients diagnosed with KD from other jurisdictions where the quality of care may be different.

CONCLUSION

In conclusion, the long-term prognosis of KD patients remained favorable with excellent survival and low incidence of all cardiovascular outcomes. Further studies are needed to determine if KD patients are truly at increased risk for hypertension compared to population comparators.

DATA AVAILABILITY

The study data set is held securely in the coded form at ICES. Although legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and governments) prohibit ICES from making the data set publicly available, access might be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS or via email (das@ices.on.ca). The full data set creation plan and underlying analytical code are available from the authors on request, understanding that the computer programs might rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or require modification.

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AUTHOR CONTRIBUTIONS

J.J.Y.L. designed the study, completed the statistical analyses, interpreted the data, and drafted the manuscript. B.W.M. and R.S.M.Y. designed the study, acquired the data from the original patient cohort, provided guidance on the analysis and interpretation of data, provided feedback on the manuscript, and revised it critically for important intellectual content. B.M.F. and J.W. designed the study, provided guidance on the analysis and interpretation of data, provided feedback on the manuscript, and revised it critically for important intellectual content. P.L. provided feedback on the study design, prepared the data sets and initial statistical analyses, provided statistical support, and revised the manuscript critically for important intellectual content. All authors were involved in the critical analysis of the final version of the manuscript. All authors approved the 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.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional ethics approval was obtained from SickKids, Toronto, Canada. The use of the data was approved by the ICES Privacy and Legal Office. Informed consent to participate in this project was not required for this study. ICES is a "Prescribed Entity" under the Personal Health Information Protection Act (PHIPA), which permits the collection of information without patient consent as ICES has policies and procedures in place to protect the privacy and confidentiality of patients as required by the Act (s.45(3)).

ADDITIONAL INFORMATION

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