Table 1
Characteristic of the included studies

Study	Year	Country	Study type	Characteristics of patients
Amadari et al	2020	Iran	Retrospective	Hospitalized patients with COVID-19
Yuan et al	2020	China	Retrospective	Hospitalized patients with concurrent COVID-19 and coronary artery disease
Chow et al	2020	United States	Retrospective	Hospitalized patients with COVID-19

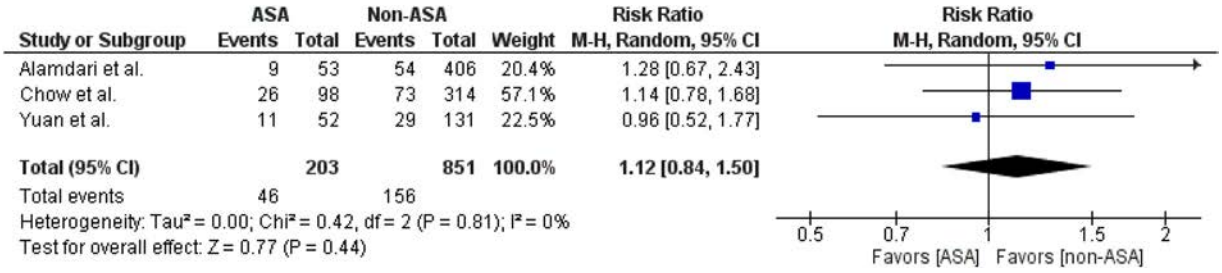

Figure 1. Forest plot examining the association between the use of aspirin and mortality in COVID-19 infection. ASA = aspirin; CI = confidence interval; M-H = Mantel-Haenszel.

Disclosures

The authors have no conflict of interest to disclose.

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High Birth Prevalence of Congenital Heart Diseases in Conjoined Twins and Higher Order Multiple Births

The birth prevalence of congenital heart disease (CHD) in the general population is 8 in 1,000 live births. In the United States, twins and triplets occur in approximately 1 in 80 and 1 in 8,000 pregnancies, respectively.[1,2] Congenital heart defects are more common in twins than in singletons, and there is an increased occurrence in monochorionic twins compared with dichorionic twins.[3–5] There is limited information on the prevalence of CHD in conjoined twins and no information on higher-order multiple births. In this study, we report the prevalence of CHD in conjoined twins as well as in triplets and higher-order multiple births in the United States.

We performed a retrospective nationwide study utilizing the Kids' Inpatient Database (KID), which was provided by the Healthcare Cost and Utilization Project (HCUP). The KID includes data from more than 3 million births annually. The KID is published every 3 to 4 years, with 2016 being the most recent year currently available. Our analysis includes data from the periods 2003, 2006, 2009, 2012, and 2016. All newborns (singleton, twins, higher-order multiple births) were analyzed.

Congenital heart diseases were identified through ICD-9 and ICD-10 codes as previously described.[6] In our analysis severe CHD included truncus arteriosus, transposition of great arteries, double outlet right ventricle, tetralogy of Fallot, hypoplastic left heart syndrome, other single ventricle lesions, atrioventricular septal defect, pulmonary atresia, tricuspid atresia, interrupted aortic arch, and total anomalous pulmonary venous return. We excluded congenital heart block, pulmonary arteriovenous malformation, anomalies of peripheral vascular system, and other specified anomalies of the circulatory system. We further excluded patent ductus arteriosus (PDA), patent foramen ovale (PFO), and secundum atrial septal defect (ASD) from the CHD list for 2 reasons: (1) PDA can be present after the first 24 hours of life in healthy children, and (2) there is not a precise way to differentiate PFO from secundum ASD using this administrative database.

Table 1
The prevalence of singleton and multiple births with and without congenital heart disease*

Variables	Singleton		Twins		Conjoined twins		Triplets and higher order	
	Total number	Birth prevalence	Total number	Birth prevalence	Total number	Birth prevalence	Total number	Birth prevalence
Total	18,923,847	96.7%	619,722	3.2%	238	0.0012%	25,967	0.13%
CHD	151,331	0.8%	14,558	2.35%#	64	27%	1324	5.1%#
Severe CHD	23,956	0.13%	1,471	0.24%#	22	9.2%	83	0.32%#

* Data points represent individual newborns, not pregnancies. Conjoined twins are considered as two individuals.
# The prevalence of congenital heart disease (CHD) and severe CHD were significantly higher in twin births and triplets and higher order births compared to singletons (p value <0.001 for both). Similarly, the prevalence of CHD and severe CHD were significantly higher in triplets and higher-order multiplets when compared to twin newborns, with p value <0.001 and 0.008, respectively. Survey-weighted Chi-square tests were performed to evaluate the statistical differences.

We retrieved 19,569,536 newborn records with in-hospital birth during our study period: 18,923,847 singletons, 619,722 twins (including 238 conjoined twins), and 25,967 triplets and higher-order multiplets. The birth prevalence of twins, conjoined twins, and higher order multiple births were similar to previously reported in the literature (Table 1).

The prevalence of CHD of any type was 8.5 per 1,000 births, and 8 per 1,000 in singleton births. The CHD prevalence in twins was 23.5 per 1000 births and was similar to previous reports ranging from 14 to 43 per 1,000 births.[4,7] In triplets and higher-order multiplets, the prevalence was 51 per 1,000 births, significantly higher than in singletons and twins (p <0.001). For conjoined twins, the prevalence of all CHD was 27 per 100 births (Table 1). Similarly, the birth prevalence of severe CHD was higher in triplets, higher-order multiplets, and conjoined twins (Table 1).

One in 4 conjoined twins was born with CHD. As monozygosity is considered a key risk factor for CHD in twins, the higher prevalence of CHD in conjoined twins is not totally unexpected.[8] It is also well known that monochorionic twins affected by twin-to-twin-transfusion syndrome (TTTS) develop valvular lesions and have a higher incidence of CHD.[9–11] It is possible that the impact of hemodynamics with a shared placenta during early gestation is a major contributing factor for CHD development. On the other hand, the reason behind the higher prevalence of CHD in triplets and higher order multiples is less clear and may be partly due to fertility treatment including in vitro fertilization,[12] unrecognized monozygosity, or ascertainment bias associated with increased level of testing likely in the setting of higher incidence of premature birth.

These data are useful from a population standpoint but are nonetheless limited in a few respects. The database unfortunately does not provide chorionicity or zygosity information. Also, ICD-9 does not differentiate triplets versus quadruplets/quintuplets/septuplets, so we had to group all these higher-order multiples into a single group. Finally, data from birth records may not account for pregnancies with multiple gestations that resulted in fetal demise.

In conclusion, conjoined twins, as well as triplets and higher-order multiplets are at significantly higher risk of CHD and severe CHD than singletons. Our data support recommendations for prenatal evaluation with detailed ultrasound and fetal echocardiogram, as well as careful postnatal evaluation by detailed physical exam and cyanotic CHD screening in order to diagnose CHD in a timely fashion and to provide appropriate perinatal management.

Declaration of Interest Statement

All authors declare they do not have conflict of interests to declare.

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