

Epidemiology of Congenital Heart Disease in Kazakhstan: Data from the Unified National Electronic Healthcare System 2014-2021

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Abstract

The aim of this study was to investigate the epidemiology of congenital heart disease (CHD) in Kazakhstan, using the data from the Unified National Electronic Healthcare System (UNEHS) for the period of 2014-2021. This retrospective cohort study included all patients diagnosed with CHD in Kazakhstan and registered in the UNEHS between January 2014 and December 2021. CHDs were defined based on ICD-10 codes Q20-Q26. Incidence, prevalence, and all-cause mortality rates were calculated per 100,000 population. Survival analysis was performed using Cox proportional hazards regression modeling and Kaplan-Meier method. The cohort consisted of 68,371 CHD patients, of whom 61,285 (89.6%) had a single CHD type, 40,767 (59.6%) were diagnosed before the age of 1 year, and 5,225 (7.6%) died over the study period. Incidence of CHD decreased from 64.6 to 47.3 cases per 100,000 population in males, and from 68.7 to 42.5 cases in females between 2014 and 2020. All-cause mortality rates per 100,000 population increased from 3.3 to 4.7 cases among males, and from 2.7 to 3.7 among females between 2014 and 2020. Survival analysis showed that in patients diagnosed with CHD before 1 year of age, risk of death was significantly associated with male sex (hazard ratio [HR] 1.17), multiple CHD types (HR 1.70), and no performed surgery (HR 0.57). In patients diagnosed with CHD after 1 year of age, risk factors were male sex (HR 1.65), multiple CHD types (HR 1.55), and no performed surgery (HR 1.82).

Keywords: Big Data, Epidemiology, Heart Defects, Congenital, Kazakhstan.

Introduction

Congenital heart disease (CHD) is a condition present at birth, which can be defined as a structural malformation of the heart or great vessels [1]. CHD is the most common congenital condition reaching an estimated incidence of 17.9 cases per 1,000 live births [2]. In 2017, a global estimate of CHD prevalence reached 11,998,283 people, which corresponds to an age-standardized prevalence rate of 170.6 cases per 100,000 population [3]. Over 97% of children diagnosed with CHD survive beyond the age of 18 years, but the risk of death before the age of 68 years for this

population is around 3.2 times higher, compared to people without CHD [4]. Across geographical regions, the highest incidence rates of CHD were observed in lower-income countries in Africa and Asia, reaching over 30 cases per 1,000 population in Central African Republic (33.8), Burundi (30.6), and Somalia (31.9). Conversely, the lowest incidence rates were under 10 cases per 1,000 population and were found in the higher-income countries like France (8.6), Portugal (6.7), and Qatar (6.2) [2]. Approximately 35% of CHD cases are diagnosed after infancy, up until late adulthood [5].

According to the systematic analysis for the Global Burden of Disease Study 2017 by Zimmerman et al. [3], the estimated number of deaths attributable to CHD in 2017 was 261,247, a 34.5% decrease from the estimated 398,580 deaths in 1990. Out of those, 180,624 (69%) deaths occurred in infants under the age of 1 year, which corresponds to 131.0 deaths per 100,000 infants in 2017. Infant mortality rates were the lowest in high income regions, such as Western Europe with 29.2 deaths per 100,000 infants, and Australasia with 26.3 deaths per 100,000 infants. The highest mortality rates were documented in North Africa and Middle east at 211.7 deaths per 100,000 infants, and in Oceania at 226.4 deaths per 100,000 infants. Age-standardized mortality in individuals of all ages decreased from 6.3 to 3.9 deaths per 100,000 population between 1990 and 2017, which constitutes a 39.0% decrease.

Although epidemiological data on the hospitalized CHD patients, especially in pediatrics cohorts, are now widely reported in both high-income and developing countries, there is little research done in Kazakhstan using such data. One example is the study by Sermanizova et al. [6]. There, it was found that the incidence of CHD in newborns under 1 year had been steadily increasing across the country from 4.4 cases per 1,000 population in 2003 to 8.9 in 2012. However, this study dealt only with the incidence of CHD in Kazakhstan in children under 5 years of age, regional variation of incidence, and categorization by CHD types. To better understand the epidemiology of CHD in Kazakhstan, further research is required.

In 2014, the unified national electronic health system (UNEHS) was established in Kazakhstan, which created a unique opportunity to study various health conditions on a national scale, including CHD. UNEHS aggregates patient data from various electronic sources, such as inpatient electronic registries of hospitalized patients, outpatient electronic registries of dispensary patients, and others, used by medical facilities in the country. Hence, the aim of this study is to explore the incidence, prevalence, all-cause mortality, and survival patterns of patients with CHD in Kazakhstan from 2014 to 2021 using patient data from the UNEHS.

Materials and Methods

Study population

This is a retrospective cohort study, which included patients diagnosed with CHD and registered in the inpatient registry of the Unified National Electronic Health System (UNEHS) between January 1st 2014 and December 31st 2021. Individual patient records containing socio-demographic and clinical data are aggregated in the UNEHS database using International Classification of Diseases 10 (ICD-10) coding. CHD were defined as ICD-10 codes Q20-26.

The patients were divided into groups of those diagnosed with a single type of CHD, and those who were diagnosed with 2 or more types, labeled 'single and 'multiple', respectively.

Exposures and covariates

Patients' records extracted from the UNEHS database contained the following information: date of birth, sex, date of diagnosis, ICD-10 codes for the main diagnosis, date of death, dates of admission and discharge, date of surgery, type of surgery, and an anonymized population registry number (RPN). Where appropriate, the date of death was retrieved using RPN's linkage with the Population Registry. Age was divided into 2 categories: under 1 year, and more than 1 year old at the time of earliest CHD diagnosis.

Outcome assessment

For each year of follow-up between 2014 and 2021, incidence, period prevalence, and all-cause mortality were analyzed for CHD patients. The incidence rate per 100,000 population was derived by dividing the number of incident cases in a year by Kazakhstan's total population of all ages in that year. Similar to this, the number of patients surviving at the end of a year and the number of fatalities in that year were divided by the total population at risk, respectively, to determine period prevalence and mortality rates per 100,000 population. Population statistics were procured from Taldau Statistics [7]. The follow-up period was defined as the period from the date of CHD diagnosis to December 31st, 2021, or until the date of death.

Statistical methods

For categorical variables, data are summarized as patient numbers and percentages. The median and interquartile range (IQR) are used to summarize continuous variables. Chi square and Mann–Whitney U tests were used for bivariate analysis. Cox proportional hazards regression modeling and the Kaplan-Meier method were used for survival analysis. Cox modeling was used to produce crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI). Separate Cox regression models were built for patients of age below and above 1 year. This was done due to a significant interaction between age at diagnosis and most other predictors. The Kaplan-Meier method was used to calculate survivor functions for CHD patients based on age at diagnosis, sex, number of malformations, surgery, and residence. The log-rank test was used to determine the significance of the difference between the survival curves.

All statistical analyses were performed using STATA 15 MP2 Version (STATA Corporation, College Station, TX). P values are two-sided and reported as statistically significant at ≤ 0.05 for all analyses. Nazarbayev University Institutional Research Ethics Committee (NU-IREC) approved this project to be exempt from further NU IREC oversight (NU-IREC 505/06122021). The study was performed according to both international and local ethics guidelines and regulations as well as declaration of Helsinki.

Results

General characteristics of the cohort

The final cohort consisted of 68,371 patients diagnosed with CHD. Among them, 61,285 were diagnosed with a single CHD type, while 7,086 were diagnosed with multiple CHD types (ranging from 2 to 7). In Table 1, the cohort's demographic details are shown. The median age at diagnosis of the cohort was 0.3 (0.0 - 7.5) years, with a higher median age among patients with a single type of CHD, compared to the patients with multiple CHD types. Among the patients, 59.6% were diagnosed with CHD within the first year of life. Moreover, almost 80% of cases with multiple CHDs were diagnosed in children under 1 year of age. Regarding surgical interventions, a statistically significant difference was also revealed. In cases with multiple CHDs, the presence of surgical interventions was 40%, compared to the 34.7% in cases with a single CHD. The percentage of deaths among multiple CHDs reached 11.5%, compared to 7.2% in the single CHD group.

The most common cardiac defects among single CHD were atrial septal defect (ASD) (25.9%), ventricular septal defect (VSD) (21.3%), and patent ductus arteriosus (PDA) (12.0%) (Table 2).

Table 1

Baseline characteristics of patients with CHD registered in UNEHS in 2014-2021

	Total	Single CHD	Multiple CHDs	p-value
Total	68,371 (100.0)	61,285 (89.6)	7,086 (10.4)	
Sex, N (column %)				
Female	34,809 (50.9)	31,240 (51.0)	3,569 (50.4)	0.332
Male	33,562 (49.1)	30,045 (49.0)	3,517 (49.6)	
Age at diagnosis, years median (IQR)	0.3 (0.0 – 7.5)	0.4 (0.0 – 8.9)	0.1 (0.0 – 0.6)	<0.001
Age at death, years median (IQR)	0.7 (0.2 – 19.8)	0.8 (0.2 – 30.9)	0.3 (0.1 – 1.2)	<0.001
Age at diagnosis, N (column %)				
<=1 year	40,767 (59.6)	35,230 (57.5)	5,537 (78.1)	<0.001
>1 year	27,604 (40.4)	26,055 (42.5)	1,549 (21.9)	
Residence, N (column %)				
Urban	44,196 (64.6)	39,612 (64.6)	4,584 (64.7)	0.927
Rural	24,175 (35.4)	21,673 (35.4)	2,502 (35.3)	
Surgery, N (column %)				
No	44,261 (64.7)	40,009 (65.3)	4,252 (60.0)	<0.001
Yes	24,110 (35.3)	21,276 (34.7)	2,834 (40.0)	
Number of surgeries, median (IQR)	1 (1 – 2)	1 (1 – 2)	2 (1 – 3)	<0.001
Death				
No	63,146 (92.4)	56,874 (92.8)	6,272 (88.5)	<0.001
Yes	5,225 (7.6)	4,411 (7.2)	814 (11.5)	

Abbreviations: CHD - congenital heart disease, IQR - interquartile range.

Table 2

The most common congenital heart defects among patients registered in UNEHS in 2014-2021

Diagnoses with the corresponding ICD-10 codes	Number of patients with the given diagnosis as a single malformation, N (%)	Number of patients who received surgical interventions with the given diagnosis, N (%)
Q21.1 Atrial septal defect	15,849 (25.9)	7,712 (32.0)
Q21.0 Ventricular septal defect	13,025 (21.3)	6,066 (25.2)
Q25.0 Patent ductus arteriosus	7,372 (12.0)	3,842 (15.9)
Q24.8 Other specified congenital malformations of heart	4,846 (7.9)	751 (3.1)
Q21.8 Other congenital malformations of cardiac septa	2,956 (4.8)	268 (1.1)
Q20.8 Other congenital malformations of cardiac chambers and connections	2,559 (4.2)	234 (1.0)
Q24.9 Congenital malformation of heart, unspecified	2,383 (3.9)	399 (1.7)
Q21.3 Tetralogy of Fallot	1,692 (2.8)	1,095 (4.5)
Q22.1 Congenital pulmonary valve stenosis	1,080 (1.8)	953 (4.0)
Q21.2 Atrioventricular septal defect	913 (1.5)	530 (2.2)

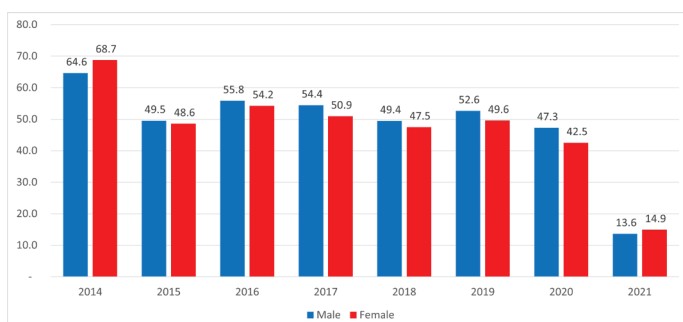


Figure 1 - Incidence rate per 100,000 population stratified by sex & year of diagnosis for CHD cohort registered in UNEHS in 2014-2021

Among them, surgery was performed on 32% of the ASD patients, 25.2% of the VSD patients, and 15.9% of the PDA patients.

Incidence, prevalence, and mortality

The incidence of CHD has decreased between 2014 and 2020 from 64.6 to 47.3 cases per 100,000 population in males, and from 68.7 to 42.5 cases in females. The estimates for 2021 are significantly lower, reaching 13.6 and 14.9 cases per 100,000 for male and female populations, respectively (Figure 1).

The period prevalence increased from 66.3 male and 71.0 female prevalent cases per 100,000 population in 2014 to 342.5 male and 339.2 female cases per 100,000 population in 2021 (Figure 2).

In terms of mortality, there is a steady increase between 2014 and 2020, whereby the rates per 100,000 population rise from 3.3 to 4.7 cases among males, and from 2.7 to 3.7 among females. Similar to the incidence, the mortality for 2021 are lower than those for earlier years, dropping to 1.1 male and 0.7 female cases per 100,000 population (Figure 3).

Given in Figure 4 are the incidence and mortality rates per 100,000 median population in Kazakhstan in the period between

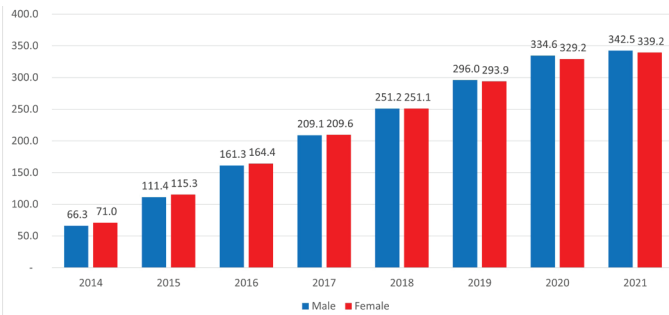


Figure 2 - Period prevalence rate per 100,000 population stratified by sex & year of diagnosis for CHD cohort registered in UNEHS in 2014-2021

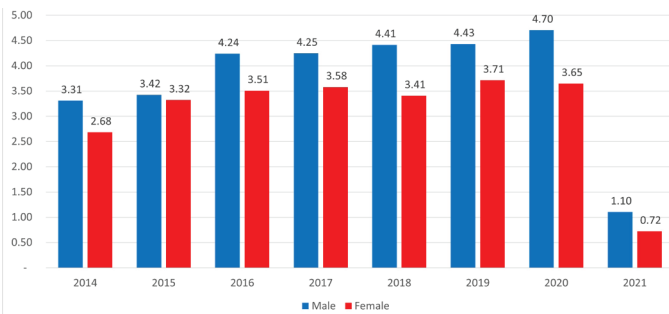


Figure 3 - Mortality rate per 100,000 population stratified by sex & year of death for CHD cohort registered in UNEHS in 2014-2021

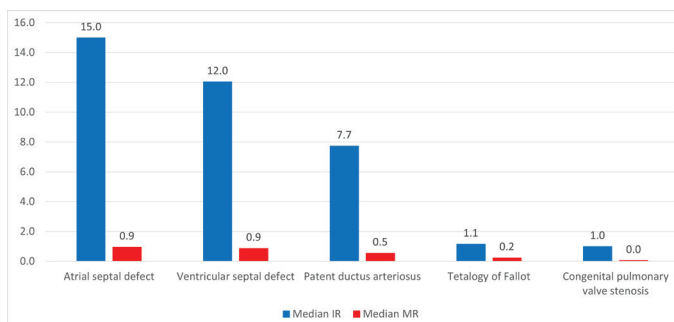


Figure 4 - Median incidence and mortality rates of most common diagnosed CHD types for CHD cohort registered in UNEHS in 2014-2021

2014 and 2021 for 5 most common specific CHD types: ASD, VSD, PDA, tetralogy of Fallot (ToF), and congenital pulmonary valve stenosis (CPVS), listed in the decreasing order of prevalence. Incidence rates are 15.0 for ASD, 12.0 for VSD, 7.7 for PDA, 1.1 for ToF, and 1.0 for CPVS per 100,000 population. Mortality rates are 0.9 for ASD, 0.9 for VSD, 0.5 for PDA, 0.2 for ToF, and <0.1 for CPVS per 100,000 total population in Kazakhstan.

Table 3

Cox proportional hazards regression models of associations between risk factors & risk of all-cause death for CHD cohort registered in UNEHS in 2014-2021 diagnosed before 1 year of age

	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex				
Female	Ref.		Ref.	
Male	1.02 (0.94 – 1.09)	0.679	1.17 (1.04 – 1.32)	0.007
Malformation type				
Single	Ref.		Ref.	
Multiple	1.69 (1.54 – 1.85)	<0.001	1.70 (1.51 – 1.92)	<0.001
Surgery				
Yes	Ref.		Ref.	
No	0.47 (0.44 – 0.51)	<0.001	0.57 (0.51 – 0.63)	<0.001
Residence				
Urban	Ref.		Ref.	
Rural	1.69 (1.57 – 1.81)	<0.001	1.22 (0.90 – 1.67)	0.205

Abbreviations: CI - confidence interval, HR - hazard ratio.

Survival analysis

Significant differences in the risk of death are observed in patients diagnosed with multiple CHD compared to those with a single CHD (HR: 1.70, 95% CI: 1.51 – 1.92, $p < 0.001$) among those diagnosed before the age of 1 years of age. A 43% lower risk of death is observed among those who did not undergo surgical intervention compared to those who did (HR: 0.57, 95% CI: 0.51 – 0.63, $p < 0.001$). Males had a 17% higher risk of death compared to females (HR: 1.17, 95% CI: 1.04 – 1.32, $p < 0.001$) (Table 3).

Among those diagnosed after the age of 1 year of age males had a 65% higher risk of death than females (HR: 1.65, 95% CI: 1.42 – 1.95, $p < 0.001$). Those with multiple CHDs had a 55% higher risk compared to those with a single CHD (HR: 1.55, 95% CI: 1.20 – 1.99, $p = 0.001$). No performed surgery was associated with an 82% higher risk of mortality compared to those who underwent surgery (HR: 1.82, 95% CI: 1.53 – 2.18, $p < 0.001$) (Table 4).

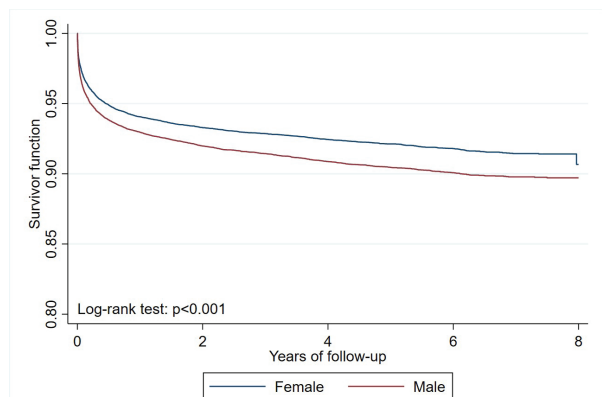


Figure 5 - Kaplan-Meier plot of survivor function stratified by sex for the CHD cohort registered in UNEHS in 2014-2021.

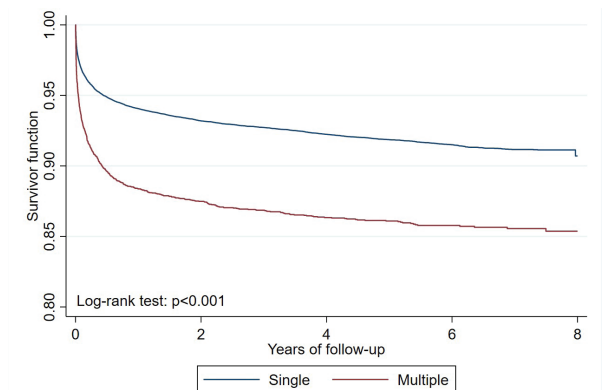


Figure 6 - Kaplan-Meier plot of survivor function stratified by the number of malformations for the CHD cohort registered in UNEHS in 2014-2021.

Table 4

Cox proportional hazards regression models of associations between risk factors & risk of all-cause death for CHD cohort registered in UNEHS in 2014-2021 diagnosed after 1 year of age

	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex				
Female	Ref.		Ref.	
Male	1.40 (1.27 – 1.56)	<0.001	1.65 (1.42 – 1.95)	<0.001
Malformation type				
Single	Ref.		Ref.	
Multiple	1.19 (0.97 – 1.45)	0.099	1.55 (1.20 – 1.99)	0.001
Surgery				
Yes	Ref.		Ref.	
No	1.65 (1.48 – 1.83)	<0.001	1.82 (1.53 – 2.18)	<0.001
Residence				
Urban	Ref.		Ref.	
Rural	1.17 (1.05 – 1.29)	0.004	0.89 (0.67 – 1.18)	0.426

Abbreviations: CI - confidence interval, HR - hazard ratio.

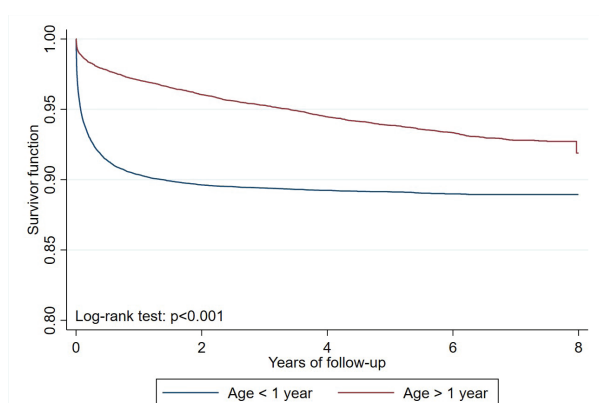


Figure 7 - Kaplan-Meier plot of survivor function stratified by age at diagnosis for the CHD cohort registered in UNEHS in 2014-2021.

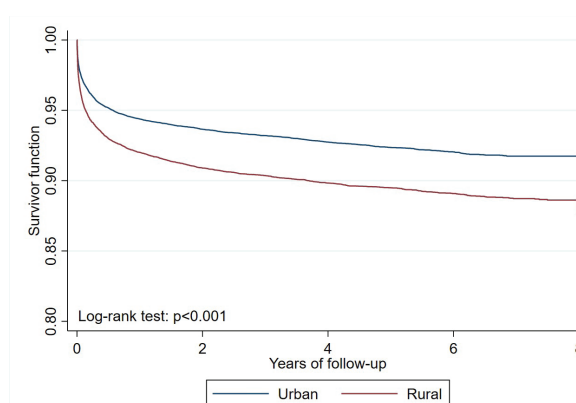


Figure 9 - Kaplan-Meier plot of survivor function stratified by residence for the CHD cohort registered in UNEHS in 2014-2021.

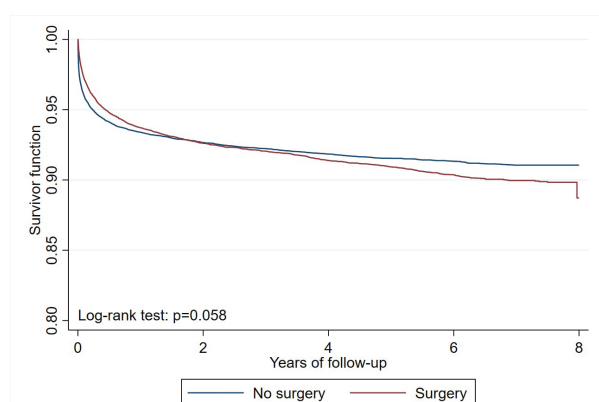


Figure 8 - Kaplan-Meier plot of survivor function stratified by surgery for the CHD cohort registered in UNEHS in 2014-2021.

Figures 5-9 depict survivor function plots constructed using the Kaplan-Meier method with the p-values from the log-rank test, indicating the significance of the difference between the survivor curves. Males exhibit generally poorer survival compared to females (Figure 5). Figure 6 shows that those diagnosed with multiple CHDs exhibit a significantly lower survival rate than those with a single CHD type. Survival in patients diagnosed before 1 year of age is significantly lower than that of patients diagnosed after 1 year of age (Figure 7). Finally, Figure 9 demonstrates that survival of rural residents is significantly lower than that of the urban residents.

Discussion

This study investigated the epidemiology of CHD in Kazakhstan. It is the first study in the Central Asian region performed on a national scale utilizing extensive administrative health data. In this study, we investigated demographic characteristics, incidence, period prevalence, all-cause mortality, and survival in CHD patients whose electronic health records were documented in the UNEHS in Kazakhstan from 2014 to 2021.

Compared to Saad et al. [8], who reported in a cross-sectional population-based study in Northern Ireland that 68% of patients were diagnosed with a single CHD type, and 32% had multiple CHD types, we found that in our cohort, 90% of the patients had single CHD types at the earliest hospitalization.

In Kazakhstan, the incidence of CHD over the study period varied between 0.65 and 0.47 for males, and between 0.69 and 0.42 for females per 1,000 live births, according to our research. This rate is considerably lower than the 4-14 per 1,000 live births CHD incidence commonly reported in large epidemiologic studies [9-11]. Since 40.4% of CHD diagnoses are made after the first year of life, the lower incidence may be explained by a potentially high prevalence of undiagnosed cases. Furthermore, the observed abrupt decrease in the number of documented cases of CHD in 2020-2021 might be explained by the burden on the healthcare system imposed by the COVID-19 pandemic and a subsequent diminished detection or capture of cases.

The challenges in comparing CHD prevalence across study results and countries owing to methodological differences are well understood [8]. Since our study cohort included people of all ages, our prevalence findings differ from those of many other studies that focused on children under the age of one. In addition, our estimates reflect period prevalence between 2014 and 2021, and do not cover cases diagnosed in earlier years due to the absence of corresponding data. Thus, a more comprehensive measure of prevalence that would encompass a longer period, would yield higher numbers.

In our study, single CHD such as ASD, VSD, and PDA were the most common. This is consistent with the findings of Liu et al. [1], where these 3 CHD types were found to account for 61% of all CHD cases worldwide. Among the patients with a single CHD type, ASD accounted for 25.9% of cases, compared to 15% globally; VSD accounted for 21.3% of cases, compared to 36% globally; and PDA accounted for 12.0% of cases, compared to 10.2% globally. Tetralogy of Fallot was found in 2.8% of the patients, compared to 4.4% worldwide [1]. The inclusion or removal of multi-code CHD in the analysis, potential variations in the inclusion of milder forms, or self-correcting forms make it difficult to draw exact comparisons [8].

In this study, the mortality rate in 2020 was 4.74 for males and 3.65 for females per 100,000 population respectively. According to Wu et al. [2], the mortality rate among CHD patients in a middle socio-demographical index (SDI) and low-middle SDI regions in 2017 were 3.5 and 4.4 per 100,000 population, respectively. The observed higher mortality rates and risks of death among male patients compared to female patients is in line with the findings by Wu et al. [2]. A higher risk of death was also observed in patients with multiple CHD types. Among the patients diagnosed before 1 year of age, the risk of death was 70% higher in those who had multiple CHDs compared to those with a single CHD type. According to Cleves et al. [12], first-year survival calculated as the percentage of the cohort decreases from 94.3% for infants with an isolated CHD to 55.6% for infants with 3 or more additional CHDs.

In infants under the age of 1 year diagnosed with CHD, the risk of death was 43% lower if no surgery was performed. Conversely, among the patients diagnosed later in life, not receiving surgery was associated with an 82% higher risk of all-cause mortality. According to Mandalenakis et al. [13], the most recent period cohort (2010-2017) had a worse outcome among children with CHD who underwent cardiac surgery, compared to earlier birth periods. The researchers concluded that this is most likely due to an increase in the detection of mild CHD conditions, which don't require treatment and have little to no effect on a child's health.

Finally, rural residence was associated with a 32% higher risk of death in the cohort, compared to urban residence. This may be attributable to higher access to healthcare facilities in urban settings, specifically because all large cardiological and

cardiac-surgical hospitals dealing with CHD are located in the cities.

This study has several limitations. Firstly, it is the use of secondary data, which is influenced by measurement accuracy and documentation practices outside of the researchers' control. Lack of information on therapies, clinical data, and instrumental data is another major problem (echocardiography, severity of the disease, etc.). It is also worth noting that in this study, to avoid double counting in calculation of most common CHDs, we only use the cases with a 'single' CHD, which constitutes 90% of the cohort. Additionally, the cohort is highly heterogeneous in terms of age due to numerous cases of CHD diagnosis late in adult life. Finally, available data covers live births only, with no data on those who have died at birth and no preterm diagnosis data.

Conclusion

The results showed an increase in the mortality and period prevalence, but not the incidence in patients with CHD. The most common congenital heart defects were ASD, VSD, and PDA, similar to the global estimates. The risk of mortality was significantly associated with male sex, multiple CHD types, and CHD-related surgery. Among infants diagnosed before the age of 1 year, the risk of death was significantly higher in cases where surgery was performed. Among the patients diagnosed later in life, the risk of death was significantly higher if no surgery was performed. Future research should be aimed at identifying additional characteristics (social, economic, clinical) that may affect the epidemiological indicators of CHD in the country.

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