Epidemiological Insights in Cornelia-de-Lange syndrome: A Systematic Literature Review

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CONCLUSION

- Cornelia de Lange syndrome (CdLS) became more commonly recognized or diagnosed over the years, as reflected by the increasing prevalence rates
- Further research is needed on CdLS mortality and risk factors which would aid in developing new diagnostic and treatment strategies

Introduction

- Cornelia de Lange syndrome (CdLS) is a severe congenital disorder affecting multiple organ systems, characterized by hirsutism, intellectual disability, prenatal/postnatal growth retardation, and distinctive facial features[1]
- CdLS is estimated to occur in 1 in 10,000 to 30,000 live births, making it a significant concern in pediatric healthcare[2]
- The disease is caused by mutations in the autosomal genes NIPBL, RAD21, and SMC3 or the X-linked genes HDAC8 and SMC1A[3]
- Understanding CdLS epidemiology is crucial for timely diagnosis and treatment

Objective

- The objective of this systematic literature review (SLR) was to investigate the incidence, prevalence, and mortality rates associated with CdLS

Methodology

- A systematic search was performed across Embase® and MEDLINE® from database inception to 2024 to identify relevant CdLS studies reporting epidemiological data
- The review followed the standard methodology for conducting SLR as per guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[4]
- The SLR encompassed a comprehensive range of study designs, including prospective and retrospective observational studies, cross-sectional analysis, and case-control investigations, to gather epidemiological data pertaining to CdLS
- A standard two independent review and quality control process was followed during data collection. The prespecified eligibility criteria is presented in **Figure 1**

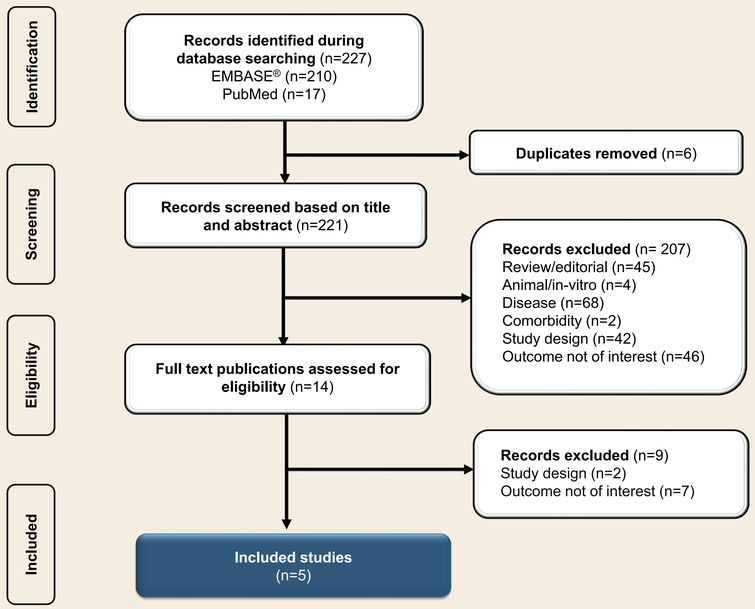
Figure 1. Eligibility criteria of the SLR

P		**POPULATION** Patients with CdLS (irrespective of age)
I & C	Rx	**INTERVENTION & COMPARATOR** No restriction
O		**OUTCOME** Incidence, Prevalence, Mortality
T		**TIME-FRAME** Database inception to 2024
S		**STUDY DESIGN** Prospective and Retrospective observational studies, Longitudinal studies, Database or registry-based studies

Results

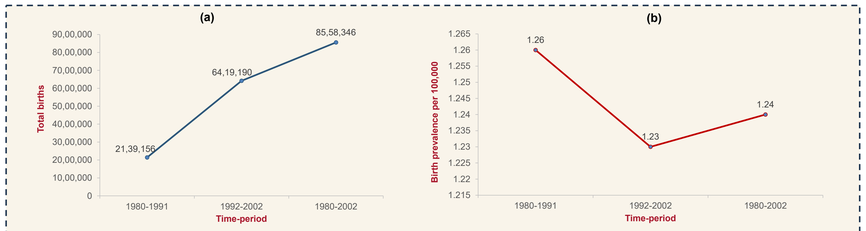
- The SLR included five of 227 screened publications (Europe=4; US=1) covering prevalence (n=3), mortality (n=2), and incidence/risk factors (n=1) **(Figure 2)**
- The population prevalence of CdLS patients ranged from 0.5/100000 in 1976[5] to 1.6-2.2/100,000 between 1980-2002[6], whereas an incidence figure of 1:50000 was reported for the years 1967-82[7]
- In the US, patients with CdLS included in the Congenital Diaphragmatic Hernia Study Group (1995-2019) had a significantly higher mortality rate compared to the general population (76% vs. 29%; $p < 0.001$)[8]
- The Spanish Collaborative Study of Congenital Malformations, conducted from April 1976 to June 1996, reported that the minimum estimate of the CdLS prevalence was 0.97 per 100,000 live births[9]

Figure 2: PRISMA diagram for the screening process



- Furthermore, the European Surveillance of Congenital Anomalies (EUROCAT) database identified 106 patients with CdLS and reported the prevalence of the classical form of the disease to be 1.24/100,000 births or 1:81,000 births in the 1980-2002 period and estimated the overall CdLS prevalence at 1.6-2.2/100,000[6]
- During this period, live-born children accounted for 91.5% (97/106) of cases, fetal deaths 2.8% (3/106), and terminations of pregnancy following prenatal diagnosis 5.7% (6/106)[6]
- The prevalence rates for the 1980-1991 and 1992-2002 time-periods were 1.26 and 1.23 per 100,000 births, respectively[6] **(Figure 3)**
- In an observational study involving 48 Danish CdLS patients, the incidence for the years 1967-82 amounted to approximately 1:50000[7]

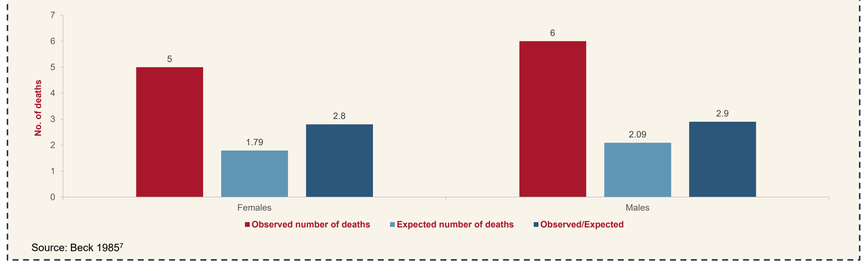
Figure 3: Prevalence of CdLS in the EUROCAT Birth Defect Registries (1980-2002 Period) (a) Total births (b) Birth prevalence



Source: Barisic 2008[6]

- Moreover, the total observed deaths were 2.8 and 2.9 times higher than expected for females and males, with raised mortality reported among the boys aged 0-4 years compared to boys aged>15 years (observed/expected number of deaths: 8.9 vs. 1.4)[7] **(Figure 4)**
- The primary causes of death were attributed to pneumonia, congenital heart defects, and gastrointestinal complications[7]

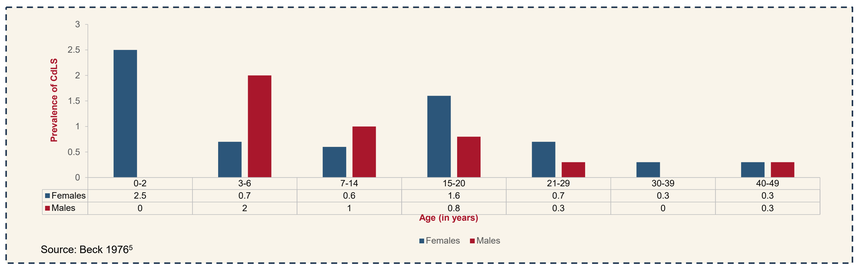
Figure 4: Number of deaths of CdLS patients compared to the expected number of deaths for the Danish population 1956-1982



Source: Beck 1985[7]

- The population prevalence of CdLS in Denmark was 0.5/100000, which remained relatively stable among individuals aged 3 to 20 years, after which it declined significantly[5] **(Figure 5)**

Figure 5: Prevalence of CdLS in the Danish population (n=24 patients)



Source: Beck 1976[5]

- Across two studies, the major anomalies associated with CdLS included limb deficiency, followed by congenital heart disease, craniofacial alterations, and genital defects[6,7]
- Additionally, severe limb anomalies occurred more significantly in males compared to females ($p=0.007$) and in patients with low birth weight ≤2,500 g ($p=0.002$)[6]

References

1. Kline et al. *Nat Rev Genet*. 2018; 19(10):649-66
2. Stryjak et al. *J Clin Med*. 2024; 13(8):2423
3. Mannini et al. *Hum Mutat*. 2013; 34(12):1589-96
4. Moher D et al., *Systematic Reviews*; 4(1): 1
5. Beck et al. *Acta Paediatr Scand*. 1976; 65(5): 631-638
6. Barisic et al. *Am J Med Genet A*. 2008; 146A(1):51-9
7. Beck et al. *Acta Paediatr Scand*. 1985; 74(5):765-9
8. Gupta et al. *J Pediatr Surg*. 2021; 56(4):697-699
9. Martínez et al. *An. pediatr*. 2023; 48(3):293-98

Sponsorship

This research is conducted solely by the authors without any collaboration from other institutes or pharmaceutical/biotech companies

Disclosures

AS, GK, and BS, the authors, declare that they have no conflict of interest

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