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ORIGINAL ARTICLE

Childhood manifestations of 22q11.2 deletion syndrome: A Finnish nationwide register-based cohort study

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Abstract

Aim: The aim of the study was to describe the clinical manifestations of 22q11.2 deletion syndrome patients in the Finnish paediatric population.

Methods: Nationwide registry data including all diagnoses and procedures of every public hospital in Finland between 2004 and 2018 along with mortality and cancer registry data were retrieved. Patients born during the study period and with an ICD-10 code of D82.1 or Q87.06 were included as having 22q11.2 deletion syndrome. A control group was formed with patients born during the study period and with benign cardiac murmur diagnosed under the age of 1 year.

Results: We identified 100 pediatric patients with 22q11.2 deletion syndrome (54% males, median age at diagnosis <1 year, median follow-up 9 years). Cumulative mortality was 7.1%. Among patients with 22q11.2 deletion syndrome, 73.8% had congenital heart defects, 21.8% had cleft palate, 13.6% had hypocalcaemia, and 7.2% had immunodeficiencies. Furthermore, 29.6% were diagnosed with autoimmune diseases, 92.9% had infections, and 93.2% had neuropsychiatric and developmental issues during follow-up. Malignancy was found in 2.1% of the patients.

Conclusion: The 22q11.2 deletion syndrome is associated with increased mortality and substantial multimorbidity in children. A structured multidisciplinary approach is necessary for managing patients with 22q11.2 deletion syndrome.

KEYWORDS
22q11.2 microdeletion, congenital anomaly, DiGeorge syndrome, immunodeficiency, velocardiofacial syndrome

1 | INTRODUCTION

The 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome, with an estimated prevalence of 1 patient for every 4000 live births.[1] The typical deletion of three megabases in the long arm of chromosome 22 is commonly *de novo* in origin, although inherited mutations are encountered occasionally.[2,3]

The 22q11.2DS is characterised by congenital cardiac defects, hypoparathyroidism, hypocalcaemia, thymic hypoplasia, varying levels of immunodeficiency, cleft palate, velopharyngeal insufficiency

Abbreviations: 22q11.2DS, 22q11.2 deletion syndrome; CI, confidence interval; CRHC, Care Register for Health Care; FISH, fluorescence *in situ* hybridisation; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; IQR, interquartile range; NCSP, Nordic Classification of Surgical Procedures; RR, risk ratio; THL, National Institute for Health and Welfare of Finland.

Ville Kytö and Johanna Lempainen contributed equally to this study.

and neuropsychiatric disorders with developmental issues. Any organ system can essentially be affected.[4] Enigmatically, the 22q11.2DS may have an unlimited variability of phenotype. Not all patients manifest the characteristic features of the syndrome, and the severity of the syndrome differs considerably among patients. In fact, even with an inherited mutation in the same family or an identical mutation in twins, the deletion can be expressed with entirely different phenotypes.[5]

Before the advent of fluorescence *in situ* hybridisation (FISH) technique for the detection of the causal deletion, the diagnosis of the syndrome was complicated by its diverse phenotype. Historically, different syndromes, such as the DiGeorge syndrome, velocardiofacial syndrome and conotruncal anomaly face syndrome,[6] were shown to be caused by the various deletion phenotypes. With the discovery of the common genetic denominator, all these syndromes can now be placed under one term: 22q11.2DS.

The diagnosis of 22q11.2DS relies on the demonstration of the loss of genetic material using either FISH or other suitable techniques. The crucial step, however, is to recognise the possibility of 22q11.2DS in patients presenting with a compatible clinical picture or a significant single feature to proceed with appropriate genetic testing. Oftentimes, the characteristic features of the syndrome have led to its diagnosis.[7,8]

After diagnosis, the multimorbidity of the syndrome must be understood so that relevant comorbidities can be screened at the right time. Given that over 180 clinical features and findings are associated with 22q11.2DS,[9] inconspicuous features may elude detection. Thus, a systematic approach in a multidisciplinary setting in managing 22q11.2DS is fundamental to achieving the best outcomes.[10]

This study analyses the childhood manifestations of 22q11.2DS in the Finnish paediatric population. The results can be utilised in designing screening for relevant comorbidities during follow-up.

Key Notes

- 22q11.2 deletion syndrome is the most common microdeletion syndrome with diverse phenotypes and outcomes.
- Studies of 22q11.2 deletion syndrome at the population level are still scarce.
- This nationwide register-based comparative analysis of paediatric patients with 22q11.2 deletion syndrome demonstrates extensive morbidity and increased mortality compared to the general paediatric population.

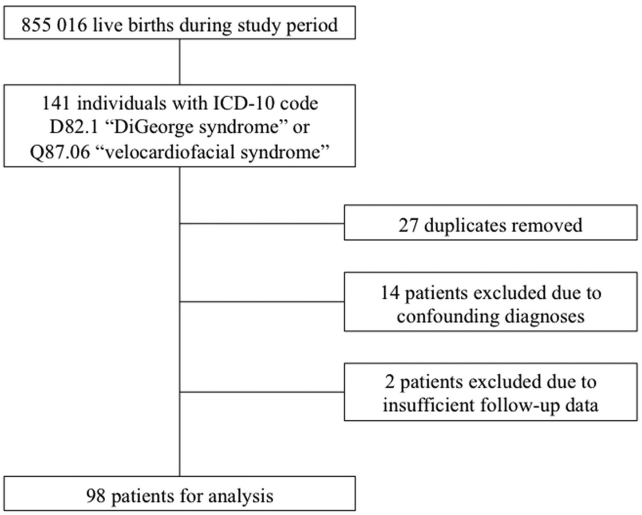

FIGURE 1 Patient selection process for 22q11.2 deletion syndrome group. Confounding diagnoses leading to exclusion were Q87.01 Acrocephalosyndactyly (Apert syndrome), Q87.03 Goldenhar syndrome, Q87.05 Moebius syndrome, Q87.10 Aarskog syndrome, Q87.16 Mulibrey nanism, Q87.27 CHARGE association, Q87.80 Alport syndrome, Q87.86 Muscle-eye-brain syndrome (MEB), Q98.0 Klinefelter syndrome, Q99.2 Fragile X syndrome.

2 | METHODS

2.1 | Study patients and design

The National Institute for Health and Welfare (THL) in Helsinki, Finland, holds a nationwide database: the Care Register for Health Care (CRHC). The CRHC records all healthcare hospital admissions, as well as outpatient and emergency visits, in every secondary and tertiary public hospitals in Finland.[11] In this register, diagnoses are based on the International Statistical Classification of Diseases and Related Health Problems, the 10th Revision (ICD-10). Procedure coding of the database relies on the Nordic Classification of Surgical Procedures (NCSP).

All individuals diagnosed with 22q11.2DS (ICD-10 code D82.1 'DiGeorge Syndrome' or Q87.06 'velocardiofacial syndrome') from 1 January 2005 to 1 December 2018 were retrospectively identified from the CRHC. Patients with a syndromatotic diagnosis considered as confounder for 22q11.2DS were excluded (Figure 1). For controls representing the general paediatric population, all individuals born during the study period diagnosed with benign heart murmur (ICD-10 code R01.0) under the age of 1 year without 22q11.2DS or any of the excluded confounder syndromes and with available follow-up data were identified from the CRHC ($n = 2964$). The ICD-10, NCSP, mortality and malignancy data of all included individuals were retrieved.[12] Follow-up started at birth and ended on 31 December 2018. The median age at follow-up was 9.0 years (IQR 6–13, range 0–15).

To study the incidence of comorbidities and procedures, the ICD-10 and NCSP codes were reviewed, after which the relevant diagnoses and procedures were grouped into analysis groups according to previous literature and clinical experience. The grouping was performed jointly by three investigators (SW, LK, and JL). The defined analysis groups are shown in Table S1 in the Supplement.

2.2 | Study data and permissions

The CRHC registry data and Finnish Cancer Registry data were obtained from the THL of Finland/Findata (permission no.: THL/164/14.02.00/2021). Mortality data were obtained from a nationwide cause-of-death registry held by Statistics Finland (permission no: TK-53-484-20). Used registries have been mandated by law, centrally collected and provided a full picture of the Finnish population.[13] Given that this study is a national retrospective registry study, hospital review board approval and informed consent were waived by the law. The participants were not contacted. The data underlying this aspect are available in Findata (www.findata.fi) with permission. National data for the number of live births were obtained from Statistics Finland (www.stat.fi). The legal basis for processing personal data is of public interest and for scientific research (EU General Data Protection Regulation 2016/679, Article 6 [1][e] and Article 9 [2][j]; Data Protection Act Sections 4 and 6).

2.3 | Statistical analysis

Differences between the study groups were analysed using the chi-squared test. Patients with 22q11.2DS were matched with the control patients at a ratio of 1:10. The nearest neighbour algorithm was used, with sex and year of birth as propensity variables. The clinical manifestations and procedures were studied using the cumulative incidence function and matched Cox regression with robust sandwich-type estimators. Cause-specific modelling was applied. The prevalence of diagnosed 22q11.2DS was calculated by dividing the number of new 22q11.2DS cases by the number of live births in Finland from 2004 to 2018. The results are given in terms of mean, percentage, relative risk (RR) or hazard ratio (HR) with a 95% confidence interval (CI) or ± SD. Statistical significance was inferred at $p < 0.05$. SAS version 9.4 (SAS Institute Inc.) was employed.

3 | RESULTS

During the study period, a total of 855 016 live births (437 313 males) occurred in Finland, and 141 patients with ICD-10 code D82.1 (DiGeorge syndrome) or Q87.06 (velocardiofacial syndrome) were identified. Among these, 27 patients had both diagnoses and were included once in the final analysis, removing 27 duplicate entries for those patients, and 14 were excluded due to confounding diagnoses, leaving 100 patients with 22q11.2DS. Patients with missing follow-up data ($n = 2$) were excluded, leaving 98 patients for analysis (Figure 1). Among all patients, 54.0% were male. Information regarding ethnicity was unavailable. The median age of diagnosis was <1 year (IQR 0–4 years; range 0–14 years). The prevalence of patients diagnosed with 22q11.2DS was 1.17/10 000 live births or 1 in every 8547 live births. The prevalence was 1.23/10000 live births in males and 1.10/10 000 live births in females (RR 1.12; CI 0.76–1.66; $p = 0.568$). Cumulative mortality during follow-up was 7.1% (HR 16.67; CI 4.86–57.20; $p < 0.0001$ vs. controls), which was clustered on the first 18 months of life and then spread fairly evenly during later childhood (Figure 2).

Among all patients with 22q11.2DS, 92.3% experienced infections that were evaluated at a secondary or tertiary centre (Table 1). Substantial infectious morbidity was also represented by a large number of tympanostomies compared with the matched controls (44.4% vs. 17.1%). The first infection diagnosis was acquired early: during the first 18 months of life, approximately two-thirds of patients with 22q11.2DS experienced their first diagnosed infection in a hospital setting (Figure 3). However, no significant difference

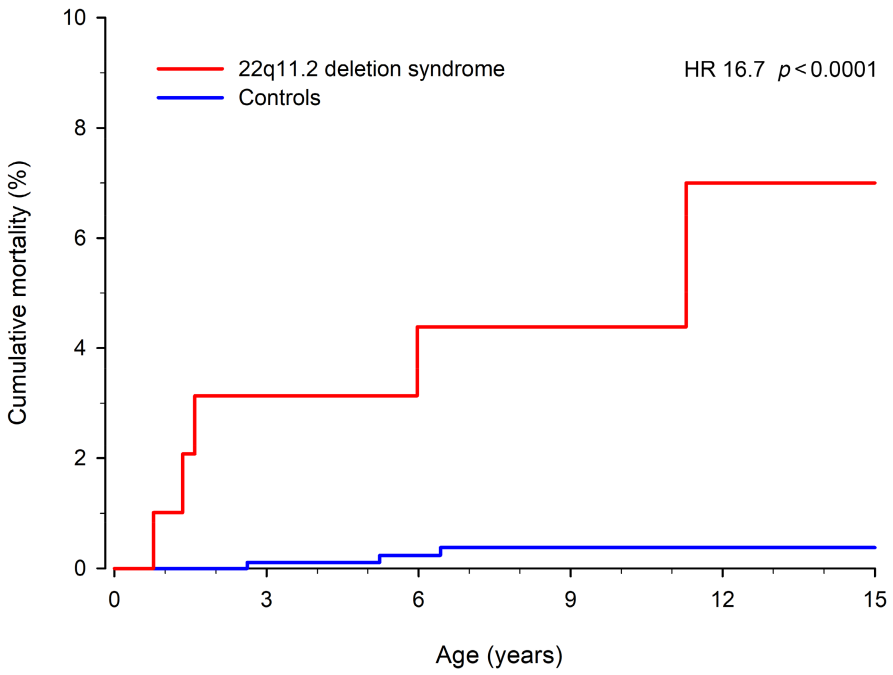

FIGURE 2 Cumulative mortality of 22q11.2 deletion syndrome patients and matched (1:10) controls.

TABLE 1 Cumulative incidence of manifestations and procedures in patients with 22q11.2 deletion syndrome and matched (1:10) controls during follow-up.

Analysis group	22q11.2DS $n = 98$	Controls $n = 980$	HR (95% CI)	p-Value
Anaemia	5.9%	2.3%	3.02 (1.16–7.89)	0.024
Atopic diseases	35.2%	26.5%	1.74 (1.23–2.45)	0.002
Autoimmune diseases	29.6%	5.0%	4.92 (2.78–8.72)	<0.0001
Cleft palates	21.8%	2.3%	9.86 (5.72–16-90)	<0.0001
Congenital cardiac defects	73.8%	10.8%	5.73 (4.51–7.30)	<0.0001
Congenital genital anomalies	14.4%	7.9%	1.68 (0.94–3.01)	0.082
Congenital GI anomalies and hernias	22.6%	9.1%	2.72 (1.74–4.25)	<0.0001
Congenital urinary tract anomalies	9.4%	1.7%	6.43 (3.13–13.20)	<0.0001
Dental disorders	49.2%	7.2%	7.60 (5.10–11.31)	<0.0001
Fractures	57.9%	22.3%	1.03 (0.55–1.90)	0.939
Hearing defects	16.6%	4.0%	5.43 (2.90–10.16)	<0.0001
Hypocalcaemia and hypoparathyroidism	13.6%	0.3%	36.67 (11.58–116.07)	<0.0001
Immunodeficiencies	7.2%	0.2%	20.00 (4.57–87.44)	<0.0001
Infections (without perinatal)	92.9%	70.3%	2.36 (1.93–2.88)	<0.0001
Malignancy	2.1%	0.6%	5.00 (1.14–21.86)	0.033
Musculoskeletal anomalies	14.7%	11.3%	1.90 (1.11–3.27)	0.020
Neurologic disorders	41.7%	9.7%	3.78 (2.53–5.66)	<0.0001
Neuropsychiatric disorders	93.2%	29.8%	14.28 (10.52–19.39)	<0.0001
Ocular disorders	47.7%	10.9%	4.55 (3.22–6.44)	<0.0001
Other ENT and ETB anomalies	95.2%	0.2%	71.83 (40.77–126.57)	<0.0001
Perinatal infections	11.2%	7.0%	1.62 (0.90–2.90)	0.107
Prematurity	23.5%	6.8%	3.65 (2.39–5.57)	<0.0001
Psychiatric disorders	20.5%	9.2%	3.91 (2.16–7.08)	<0.0001
Short stature	16.8%	5.1%	9.23 (5.00–17.05)	<0.0001
Thrombocytopenia	2.2%	0.0%	NA	<0.0001
Operations				
Cardiac procedures	35.8%	0.8%	46.90 (22.27–98.77)	<0.0001
Cleft palate and pharynx repairs	23.3%	1.9%	11.58 (6.99–19.17)	<0.0001
Dental procedures	28.9%	3.8%	6.72 (4.59–9.86)	<0.0001
Tympanostomy	44.4%	17.1%	2.58 (2.04–3.27)	<0.0001
Death	7.1%	0.4%	16.67 (4.86–57.20)	<0.0001

Abbreviations: CI, confidence interval; ENT, ear-nose-throat; ETB, esophageotracheobronchial; GI, gastrointestinal; HR, hazard ratio.

was observed in perinatal infections when compared to that in the matched controls (11.2% vs. 7.0%; $p = 0.107$) despite having a statistically significant difference in frequency of prematurity (23.5% vs. 6.8%; $p < 0.0001$).

Immunodeficiency of any degree was diagnosed in 7.2% of the study patients during follow-up (Table 1). Autoimmune diseases were diagnosed in 29.6% of the patients; these diseases were reported quite steadily from 1 year of age until 11 years of age during the peak of diagnosing autoimmune diseases (Figure 3). Atopic diseases were found in 35.2% of the patients. Diagnoses concerning anaemia and thrombocytopenia were observed in only 5.9% and 2.2% of the patients, respectively. Hypocalcaemia and hypothyroidism were diagnosed meagrely in 13.6% of the patients. Short stature occurred in 16.8% of the patients. Malignancy was found in only 2.1% of the patients.

Congenital heart defects were detected in 73.8% of the patients. This finding was reflected in the large number of cardiac procedures (35.8%) (Table 1). Cleft palate was noted in 21.8% of the patients. Repair operations of palatal and pharyngeal defects were performed in 23.3% of the patients. Dental disorders were recorded more often in patients with 22q11.2DS than in the comparison group (49.2% vs. 7.2%; $p < 0.0001$); a similar finding was also observed with dental procedures (28.9% vs. 3.8%; $p < 0.0001$). Hearing defects were detected in 16.6% of the patients. Other otorhinolaryngeal congenital anomalies grouped with oesophageal and tracheobronchial defects were discovered in 95.2% of the patients.

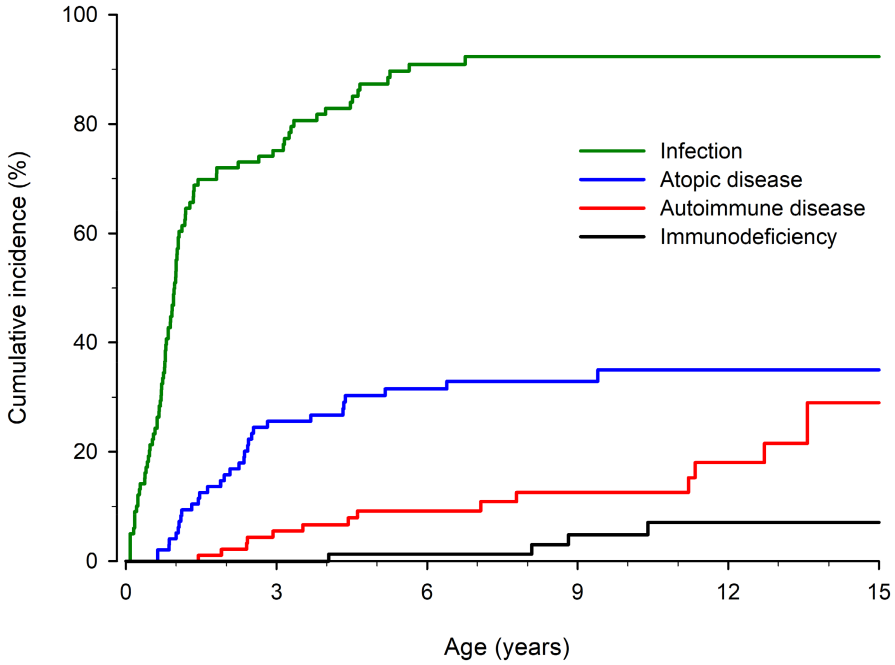

FIGURE 3 Cumulative incidence of infection, atopic disease, autoimmune disease and immunodeficiency in 22q11.2 deletion syndrome patients.

Structural anomalies and hernias of the abdominal region of the gastrointestinal tract were observed in 22.6% of the patients (Table 1). Congenital urinary tract anomalies were recorded in 9.4% of the patients. No difference in congenital genital anomalies was found between patients with 22q11.2DS and the control group (14.4% vs. 7.9%; $p = 0.082$). Congenital structural musculoskeletal defects were noted in 14.7% of the patients (HR 1.90; CI 1.11–3.27; $p = 0.020$). No significant difference in the number of fracture incidents was found in patients with 22q11.2DS compared with the matched controls (57.9% vs. 22.3%; $p = 0.939$).

Neuropsychiatric disorders, including developmental issues, were recorded in 93.2% of the patients, which was notably more than that in the control group (29.8%; $p < 0.0001$) (Table 1). Other psychiatric disorders, neurologic disorders and ophthalmologic anomalies and disorders were found in 20.5%, 41.7% and 47.7% of the patients, respectively.

4 | DISCUSSION

In this retrospective cohort study, we examined the clinical manifestations of, and procedures performed on 22q11.2DS patients in the Finnish paediatric population with nationwide registry data spanning 14 years and accumulating a large sample of 100 patients. In our study population, comorbidity was extensive and substantial in most areas when compared to that in the matched controls of individuals with benign heart murmur and without a diagnosis of 22q11.2DS or any confounding diagnoses related to it.

In our study population, mortality was moderately increased and comparable to previous publications, both in quality and quantity. The mortality rate has reached 14% in patients with 22q11.2DS.[14] Most deaths in patients with 22q11.2DS are due to cardiac defects during the first years of life, but deaths due to sepsis and respiratory failure have also been reported.[2,3,15] Reducing the mortality of patients with 22q11.2DS mainly relies on the advancement of cardiac surgery.

For the most part, the cumulative incidence of characteristic features in our study of patients with 22q11.2DS was comparable to the literature. Among them, cardiac defects, cleft palate, infection tendency and neuropsychiatric disorders have been noted.[3,7,8] By contrast, hypocalcaemia and immune deficiency diagnoses were underrepresented. For hypocalcaemia, the reason may be based on each clinician's individual habit of coding diagnoses—either the detected hypocalcaemia events are so minor that a separate diagnosis code is unnecessary or the clinician has deemed it as a part of another diagnosis, such as the 22q11.2DS. These explanations can also be applied to some of the minor features of 22q11.2DS that were noted to a smaller extent in our study than in the literature. For example, anaemia and thrombocytopenia have been described in ~33%–54%[8,16] and 35%–38%[17,18] of patients with 22q11.DS, respectively; however, most of the time, their severity is rather insignificant.[8,19]

Diagnosis of infectious diseases at least once at a secondary or a tertiary hospital was notably more frequent in patients with 22q11.2DS compared with the general population control group. This finding is probably due to the low threshold of patients with 22q11.2DS seeking medical attention. Our approach does not differentiate between mild and severe infections; however, the fact that a large number of tympanostomies were performed (at least once in 44.4% of patients) supports the notion of a true increase in early infectious morbidity, as well as the previously reported increased tendency for recurrent otitis media in patients with 22q11.2DS.[8]

For immune deficiencies, particularly immunoglobulin deficiencies, a lower number of diagnoses were clearly observed

when compared to those in the literature.[20] Importantly, however, one patient out 98 patients was diagnosed with severe combined immunodeficiency, which is consistent with the literature.[21] A lack of systematic evaluation of the immune system for every patient with 22q11.2DS may explain the low number of diagnosed immunodeficiency.

The cumulative incidence of autoimmune disorders was notably high in our study: autoimmune disorders have been observed in 10%–30% of paediatric patients with 22q11.2DS.[3,20,22] In addition to autoimmune diseases linked to 22q11.2DS, such as idiopathic thrombocytopenic purpura, juvenile rheumatoid arthritis, hypothyroidism and hyperthyroidism, our analysis group for autoimmune diagnoses included also psoriasis, both with and without joint involvement, which may partially account for the discrepancies observed with the literature.

The risk of malignancy in 22q11.2DS is increased compared to the healthy general paediatric population, albeit moderately, with a frequency of 1% in the paediatric 22q11.2DS population.[23] A predilection for lymphomatotic malignancies may occur, although malignancies of the liver, kidneys and nervous system have also been repeatedly reported.[24] In our study population, one patient was diagnosed with retinal malignancy during the follow-up period.

Our choices for forming the analysis groups varied from groups with univocally delineated medical entities, such as the cleft palate group, to groups with multifaceted clinical manifestations, such as the neuropsychiatric and developmental disorder groups. The decision behind such broad groups was intentional, as some of the single entities were too scarce to deliver a reliable notion of morbidity in either study group. As different diagnoses or procedures within an analysis group can carry an entirely different clinical significance, this decision for broad groups may overestimate the absolute burden of comorbidity for a single patient.

The fundamental strength of our study is the nationwide identification of patients with designated diagnosis codes with long-term and complete follow-up data. The main restriction of this study is due to the nature of the registry data. We have no genetic data available for confirmation of 22q11.2DS diagnoses. As genetic investigations for detecting 22q11.2DS are both readily available and employed in Finland, combined with the exclusion of confounding diagnoses from our study population, our study may unlikely suffer from a significant number of patients with a false 22q11.2DS diagnosis. The general accuracy of the CRHC was previously shown to be good,[25] and the database is widely used in outcome studies. However, we had no access to clinical data and were unable to perform confirmatory analyses on diagnoses and outcomes.

The coding practices for 22q11.2 deletion syndrome (22q11.2DS) in Finland appear to be inconsistent. In our experience, besides the specific codes of D82.1 and Q87.06, general codes such as Q93.8 (other autosomal deletions) may also be employed to code 22q11.2 deletion syndrome. In some cases, children diagnosed with 22q11.2DS who lack characteristic symptoms such as cardiac anomalies, cleft palate and immunodeficiency, may be more likely assigned these general codes. This may be especially the case for children diagnosed with 22q11.2DS due to other less severe features and milder phenotype at a later age. This may also overestimate the presence of more severe phenotypes and features and to some extent underestimate the true overall prevalence of 22q11.2DS in paediatric patients. At minimum, our findings reflect the characteristics of individuals who were diagnosed at an early age and with severe features of 22q11.2DS.

5 | CONCLUSION

The clinical manifestations and their severity in patients with 22q11.2DS can vary significantly from one individual to another. In our study, increased mortality and substantial multimorbidity in paediatric patients with 22q11.2DS were observed. A structured multidisciplinary approach to the management of patients with 22q11.2DS is necessary for the diagnosis, treatment and follow-up of these patients.

AUTHOR CONTRIBUTIONS

All authors participated in designing the study; VK had full access to all data in the study and assumed responsibility for the integrity of the data and the accuracy of the statistical analysis; all authors analysed the data; VK performed the statistical analysis; SW, VK and JL drafted the manuscript; all authors reviewed the manuscript for important intellectual content. VK and JL made equal contributions to this work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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