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Survival, hospitalisation and surgery in children born with Pierre Robin sequence: a European population-based cohort study

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TITLE PAGE

Title

Survival, hospitalisation and surgery in children born with Pierre Robin sequence: a European population-based cohort study

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Keywords

Pierre Robin sequence, health outcomes, survival, hospitalisation

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ABSTRACT

Objective. To evaluate survival, hospitalisations and surgical procedures for children born with Pierre Robin sequence (PRS) across Europe.

Design. Multi-centre population-based cohort study.

Setting. Data on 463 livebirths with PRS from a population of 4,984,793 from 12 EUROCAT congenital anomaly registries.

Methods. Data on children with PRS born 1995-2014 were linked electronically to data on mortality, hospitalisations and surgical procedures up to ten years of age. Each registry applied a common data model to standardise the linked data, and ran common syntax scripts to produce aggregate tables. Results from each registry were pooled using random effects meta-analyses.

Main outcome measures. Probability of survival, proportion of children hospitalised and undergoing surgery, and median length of hospital stay.

Results. The majority of deaths occurred in the first year of life with a survival rate of 96.0% (95%CI 93.5-98.5); 95.1% (95%CI 92.7-97.7) survived to age 10. In the first year of life, 99.2% (95%CI 95.0-99.9) of children were hospitalised with a median stay of 21.4 days (95%CI 15.6-27.2) and 67.6% (95%CI 46.6-81.8) underwent surgery. In the first 5 years of life, 99.2% of children underwent a median of two surgical procedures. Between ages 5-9, 58.3% (95%CI 44.7-69.7) were hospitalised with a median annual stay of 0.3 days.

Conclusion. Children with PRS had high mortality and morbidity with long hospital stays in the first year of life and almost all had surgery before five years of age. Survival improved after infancy with fewer hospitalisations after age five. This study provides reliable estimates of the survival and morbidity of children with PRS for families and health-care providers.

MANUSCRIPT

INTRODUCTION

Pierre Robin sequence (PRS) is a rare congenital anomaly (CA) characterised by three main clinical signs: micrognathia, glossoptosis, and obstruction of the upper airway.¹ It is frequently associated with cleft palate.²

The European network for the surveillance of CAs (EUROCAT) estimates that the total prevalence of PRS is 12.0 per 100,000 births in the populations covered by EUROCAT registries, with 94.1% being live births. Amongst the liveborn children with PRS, 72% were isolated PRS, 5% were associated with a genetic syndrome, 5% with chromosomal anomalies, and 18% with other structural CAs.³ Respiratory disorders and feeding problems represent the main burden of the disease. Upper airway obstruction can occur with different levels of severity requiring different management. Airway obstruction is most dangerous during the first month, requiring close respiratory monitoring.⁴ Feeding difficulties are thought to be secondary to both the airway obstruction and the associated cleft palate, leading to failure to thrive.⁵

Diagnosis and care of children with PRS require a multidisciplinary approach for surgical and non-surgical management.⁶⁻⁸ A review by Côté et al. reported that 68% of infants were successfully treated with non-surgical interventions (i.e. prone position, nasopharyngeal airway, orthodontic apparatus or continuous positive airway pressure).⁵ Surgical procedures used to treat infants with major respiratory obstruction are tongue–lip adhesion and distraction osteogenesis of the mandible. For the most severely affected infants, tracheostomy may be needed.^{5-7,9}

PRS is a rare disease with a high burden on affected children and their families.

The objectives of this study were:

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- To evaluate survival rates for children born with PRS across Europe
- To evaluate rates and length of hospital stays for children born with PRS across Europe
- To evaluate rates of surgical procedures performed on children born with PRS across Europe

METHODS

This is a EUROLINKCAT population-based data-linkage cohort study. The EUROLINKCAT project aimed to evaluate health outcomes in children with CAs up to ten years of age by linking data on liveborn children registered in EUROCAT registries^{10,11} to data in healthcare databases (e.g. mortality, hospital admission and discharge data). Linked data were included up to the child’s 10th birthday or to 31st December 2015 (whichever was earlier).¹² EUROCAT registries collect standardised data on all major CA cases in their population using multiple sources of ascertainment according to EUROCAT guidelines (*EUROCAT* Guide 1.5: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en#inline-nav-2). All registries with the ability and capacity to link to their mortality and hospital discharge databases were included in the EUROLINKCAT project¹²

All registries contributing data to the EUROLINKCAT project already have ethical permission and procedures in place for registering cases of CAs in their region according to their own national guidelines. Only one registry (Northern Netherlands, NNL) requires informed consent to register a child with a CA. Approximately 20% of parents in NNL do not give their consent, hence these children are not included in any study.

The study included data from 12 registries in 9 European countries (Table 1) covering different time periods between 1995 and 2014. The different time periods were due to registries having different years of EUROCAT membership and that only years with good quality healthcare data and high levels of linkage were included.¹³ Three registries (Norway, Wales and Malta) were national registries

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3 covering the whole country. Four registries covered all 20 birth years of the study period. All liveborn
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5 children with PRS during the specified birth years were included.
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8 For the investigation of survival rates, data on mortality were obtained through linkage with vital
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10 statistics and mortality databases. A detailed description of the methods has been published
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12 elsewhere.¹⁴⁻¹⁶
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15 Data on hospitalisations and surgical procedures were obtained by electronic linkage to the hospital
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17 databases used in the regions and countries covered by the registries. For three participating
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19 registries (i.e. Paris, Norway and Malta) data on hospitalisations were not available for this study.
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21 Indicators of hospitalisation in children with PRS were compared with those in a) all children born
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23 with any CA and b) reference children without a CA, previously calculated by the EUROLINKCAT
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25 project¹⁷. Reference populations were all liveborn children without CAs from the same population
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27 covered by the registry, in the same birth years. The Tuscany and Northern Netherland registries
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29 used a random sample of their population (10% and 20%, respectively). No reference children were
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31 available for the three English registries. A detailed description of the EUROLINKCAT methods on
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33 hospitalisations has been published elsewhere.¹⁷
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42 Statistical analysis

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44 The EUROLINKCAT common data model standardised the linked variables obtained by each
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46 participating registry. Common Stata syntax scripts were run by all registries to check the quality of
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48 data linkage and to analyse the data. Aggregated data and analytic results were uploaded to the
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50 Central Results Repository based at Ulster University (UK) and then transferred to the research team
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52 using a secure web platform.¹²
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56 Within each registry, Kaplan-Meier survival analyses were performed to account for censoring i.e.
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58 children who were lost to follow-up due to death or emigration from the study area or who had not
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reached their 10th birthday by 31st December 2015. The Kaplan-Meier survival estimates with 95% confidence intervals (CI) from each registry were combined in a random-effects meta-analysis using a modified method by Combes et al¹⁸ to estimate the overall survival for children with PRS at the following ages: 1 week, 4 weeks and 1, 5 and 10 years. In addition, the 10-year survival conditional on having survived at 4 weeks was estimated.

The length of stay in hospital (LOS) was calculated as the number of days spent in hospital between the date of admission and the date of discharge. For hospital stays in which the date of admission and discharge occurred on the same day, the LOS was considered to be 0.5 days. The median LOS per year, for those with at least 1 admission, was calculated within each registry and random effects meta-analyses were performed using the “metamedian” package in R (version 4.0.3) for the age groups: <1 year, 1-4 years, 5-9 years. The above methods were also used to estimate the median age at first surgery and the median number of surgical procedures for the age groups: <1 year, 1-4 years, 0-4 years.

Within each registry, estimates for the percentage of children (i) hospitalised (ii) with a hospital stay longer than 10 days; (iii) undergoing surgery; (iv) undergoing surgery for gastrostomy (permanent feeding tube); (v) being admitted for intensive care; and (vi) being on a ventilator, were estimated using Kaplan-Meier analyses. Random-effects meta-analyses were performed to provide overall estimates for age groups.

RESULTS

Survival

A total of 463 children born with PRS from 12 EUROCAT registries covering a population of 4,984,793 births between 1995 and 2014 were included in the study (Table 1). Among 463 children with PRS, a total of 26 deaths were observed during the study period. The majority of the deaths (21/26) occurred in the first year of life with an infant mortality rate of 4.0% (95%CI 1.5-6.5). Survival was 99.7% (95%CI 99.2-100.0) at 1 week, which dropped to 96.0% (95%CI 93.5-98.5) at 1 year and to 95.1% (95%CI 92.7-97.7) at 10 years of age (Table 2). The probability of surviving to 10 years of age, having survived to 4 weeks, was 96.3% (95%CI 93.5-97.9). Five-year survival estimates in the registries ranged from 84.6% (95%CI 71.6-92.0) in Valencian Region (Spain) to 100% (95%CI 66.4-100) in Tuscany (Italy). The low precision of these estimates is due to the small numbers of events (supplemental file 1).

Hospitalisations

Data on hospitalisations were available for 306 children born with PRS in 9 registries. Overall, 99.2% (95%CI 95.0-99.9) were hospitalised in the first year, decreasing to 58.3% (95%CI 44.7-69.7) at age 5-9 years (Table 3). The percentage of children with PRS who were hospitalised is higher than that for children with any CA and for the reference children (Figure 1).

In the first year of life, 66.2% (95%CI 51.8-77.1) of children with PRS had at least one hospital stay longer than 10 days, which decreased to 13.1% (95%CI 1.0-41.1) at 1-4 years (Table 3). No long hospital stays were observed after 4 years of age. Compared with children with any CA,¹⁷ these percentages are higher both in the first year of life (66.2% vs. 23.9%), and at 1-4 years (13.1% vs 5.4%).

The median LOS was 21.4 days per year (95%CI 15.6-27.2) in children <1 year, 1.0 days (95%CI 0.7-1.3) in children 1-4 years, and 0.3 days in children 5-9 years (95%CI 0.2-0.5).

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Surgery and other procedures

Data on surgery were available for 261 children born with PRS from 8 registries. Overall 99.2% (95%CI 94.4-99.9) of children underwent surgery in the first 5 years of life, while 67.6% (95%CI 46.6-81.8) had surgery in the first year (Table 4). The median number of surgical procedures in the first 5 years was 2.0 (95%CI 1.7-2.2). The median age at first surgery was 39.4 weeks (95%CI 32.1-46.4). In the first 5 years of life 5.6% (95%CI 3.0-9.4) received a gastrostomy for tube feeding.

Data on admissions to intensive care units (ICU) were available for 71 children from 7 registries. In the first five years of life 22.6% (95%CI 12.9-34.0) of children with PRS were admitted to ICU. Data on the use of mechanical ventilation were available for 192 children from 9 registries which showed that 14.3% (95%CI 8.7-21.2) of children with PRS had been on a ventilator in hospital.

DISCUSSION

This population-based cohort study reported on survival and hospitalisations of 463 children born with PRS in nine European countries, which is in contrast to many of the published studies on PRS limited to case series.¹⁹ We were not able to analyse data separately for children with isolated PRS and those with associated anomalies. However, an estimated 72% of children were likely to have had isolated PRS, as observed in a recent EUROCAT study on the epidemiology of PRS which included most of the children in this study.³

Survival

In our study mortality was highest in the first year of life, with 4.0% (95%CI 1.5-6.5) of children dying, but survival improved and 95.1% (95%CI 92.7-97.7) survived to age 10. The early months of life

represent the most critical time for children born with this rare anomaly. After infancy we observed a good prognosis for these children.

Several published studies based on PRS case series have reported an infant mortality ranging from 1.7% to 4.1% which is consistent with our estimate.²⁰⁻²³ However, other studies have reported higher mortality: Logjes et al. reported an overall mortality risk of 10% observed among about 100 patients in a hospital centre in over a 20-year period. The same study reports that mortality was associated with syndromic cases and neurological anomalies.²⁴ Another study by Costa et al. reported a mortality of 16.6% in 181 infants admitted to a Neonatal Intensive Care Unit,²⁵ a higher mortality in cases with associated anomalies and no deaths in isolated cases. The proportion of isolated cases observed in their study was lower than that observed in EUROCAT registries,³ indicating that perhaps the healthier children with isolated PRS were not admitted to the NICU and hence not included in the study.

Hospitalisation

Almost all children with PRS were admitted to hospital within the first year of life. The 0.8% without a hospital admission may have died shortly after birth and/or were not linked to the hospital databases. Hospital admissions reduced with age, but 60% of the children had at least one hospital admission at age 5-9 years with a much shorter median LOS was compared to children admitted in the first year of life. The number of hospitalisations of children with PRS exceeded those for all children with any CA at all ages.

Stubenitsk et al. reported that LOS was higher in children with respiratory disorders and feeding problems.²⁶ A study by Lee et al. on infants admitted to a tertiary referral centre with failure to thrive due to airway obstruction or feeding difficulties reported an average primary LOS of 64 days.⁸

The widely different results between our study and the Lee study can be explained by the facts that

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the mean is calculated (rather than the median) and our cohort was population-based, including all children with PRS, not just those admitted to a tertiary centre.

Surgery

Several studies have found that about 70% of children with PRS were successfully managed conservatively, by use of appropriate positioning, without the need for early surgical treatment for airway obstruction.^{5,7,27} Surgical treatment is needed for infants with moderate or severe airways obstruction who do not respond positively to positioning or other non-surgical treatments.^{5,6} In our cohort we observed that 67.6% of the children underwent surgery in the first year of life. Not all these children had surgery for airway obstruction as some children may have had surgery for closure of a cleft palate, which occurs in about 90% of children with PRS.³ There is no clear consensus about the optimal age for surgery for cleft palate, as early surgery may have a negative impact of the maxilla and late surgery may be associated with speech delays and difficulties.^{28,29} Overall 99% of the children in our study underwent surgery at least once before the age of 5 years and 61.1% after the first year. This proportion presumably included many operations for cleft palate.

Severe airway obstruction is associated with failure to thrive in children with PRS. Children with severe feeding difficulties who have failed to respond to conservative measures sometimes need the placement of gastrostomy tubes.³⁰ This procedure is less frequently used in isolated PRS.³¹ In our cohort, a gastrostomy was needed for 5.6% of children with PRS.

About 23% of the children were admitted to ICU and 14% needed a ventilator within the first five years. These children may represent the proportion of patients with major respiratory complications. These proportions are likely to be under-estimated as there were some difficulties in defining the treatment codes used for the registration in the hospital databases. Furthermore, we

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3 didn't have information about home mechanical ventilation. We are not aware of other studies that
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5 investigated ICU admissions or mechanical ventilation use.
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8 Effective and timely clinical management, including an appropriate surgical treatment, is
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10 fundamental to ensure an adequate level of quality of life especially during childhood and
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12 adolescence.^{6,32}
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17 **Strengths**

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19 The main strength of this study is the population-based setting which allows the inclusion of all
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21 children born with PRS and not only children referred to tertiary care centres as considered in many
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23 existing studies. Additionally, information on children with PRS were collected and validated by
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25 EUROCAT registries which have high levels of case ascertainment and use standardised definitions
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27 and coding of CAs to ensure consistency across Europe.
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34 **Limitations**

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36 A limitation of the study is that isolated cases and associated cases of PRS could not be analysed
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38 separately due to the very small sample size in most of the registries. For the same reason analyses
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40 by different time periods could not be performed.
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44 Another limitation is that failure of linkage, occurring when an individual fails to be matched with
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46 the records in the healthcare databases or is matched to the wrong record, could have produced
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48 bias in some outcomes. However, linkage failure is most likely to occur in the first days of life before
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50 the newborns have their permanent name or Identification number¹³. As children with PRS have a
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52 high survival rate in the first days of life, the impact of this limitation is likely to have been minimal.
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CONCLUSIONS

Our study showed that the 10-year survival rate for children with PRS in Europe was more than 95%. However, these children have high morbidity, long hospital stays in the first year require surgery before 5 years of age. About one in five of the children have at least one admission to intensive care, one in ten will need mechanical ventilation at least once, and one in twenty will need surgery for a permanent feeding tube. All these challenges carry inherent risks of complications and are a major burden for the child and the family. Efforts must be done to support these families throughout these children’s childhood.

What is already known on this topic

- Pierre Robin sequence (PRS) is a rare congenital anomaly with a prevalence of 12.0 per 100,000 births
- Respiratory disorders and feeding problems represent the main burden of the condition
- Many studies on PRS are limited to case series and often include only children referred to tertiary centres

What this study adds

- This study is a population-based multicentre study of about 500 children born with PRS
- In the first year of life, 4.0% (95%CI: 1.5-6.5) of children died, but survival improved and 95.1% (92.7-97.7) survived to age 10 years
- 99% of children with PRS had surgery before 5 years of age

How this study might affect research, practice or policy.

- Results on several health outcomes provides information to evaluate the burden of PRS
- Health outcome indicators provide useful information to support the healthcare system and the clinical management of children with PRS.

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Contributors MS, EG, AC, JT, ML and JM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: MS, EG, AC and JM.
Development of study methods, including data standardisation and linkage, development of statistical analysis plan, writing analysis programs and statistical analysis: ML, MS, AC, JM, JT, EG.
Data acquisition and interpretation of the results: All authors.
Drafting of the manuscript: MS, EG and JM.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: JM, EG, ML.
Supervision: JM.
All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

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Competing interests None declared.

Patient consent for publication Not required.

Data availability statement The data that support the findings of this study are available from the participating registries of congenital anomalies, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors for scientifically valid requests and with permission of the participating registries of congenital anomalies.

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TABLES AND FIGURES

Table 1. European Surveillance of Congenital Anomalies (EUROCAT) registries, birth years included, population covered, and number of children with Pierre Robin sequence (PRS)

Participating registries	Included birth years	Birth population covered ^a	Number of children with PRS
Denmark: Funen	1995-2014	105,770	10
France: Paris ^b	1995-2014	597,822	87
Italy: Emilia Romagna	2008-2014	282,094	15
Italy: Tuscany	2005-2014	299,869	9
Malta ^{b,f}	1995-2014	84,737	10
Netherlands: Northern	1995-2014	372,192	45 ^e
Norway ^{b,f}	1999-2014	956,939	35
Spain: Valencian Region	2007-2014 ^c	403,099	52
UK: East Midlands and South Yorkshire	2003-2012	717,264	47
UK: Thames Valley	2005-2013	270,327	34
UK: Wales ^f	1998-2014	569,341	110
UK: Wessex	2004-2014	325,339	^d
Total		4,984,793	463

^a extracted from the EUROCAT website: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en, accessed on 30/09/2021

^b data on hospitalisation not available

^c study period for hospitalisation 2010-2014

^d not available due to small numbers

^e number was rounded to the nearest 5 for the Northern Netherlands

^f whole nation covered

Table 2. Pooled survival estimates at selected age groups up to 10 years of age for children born with Pierre Robin sequence (n=463), 1995-2014

Age	N. of deaths	Survival %	95%CI
1 week	1	99.7	99.2-100
4 weeks	7	98.8	97.6-100
1 year	21	96.0	93.5-98.5
5 years	26	95.3	92.9-97.7
10 years	26	95.1	92.7-97.7
10-year conditional on surviving to 4 weeks	19	96.3	93.5-97.9

Table 3. Percentage hospitalised, percentage with a long hospital stay (≥10 days) and median length of stay per year of children with Pierre Robin sequence (n=306), by age, 1995-2014

age	Children with any hospitalisation			Children with a length of stay over 10 days ^a			Median length of stay	
	n	%	95%CI	n	%	95%CI	days	95%CI
<1 year	293	99.2	95.0-99.9	127	66.2	51.8-77.1	21.4	15.6-27.2
1-4 years	213	76.7	64.3-85.2	12	13.1	1.0-41.1	1.0	0.7-1.3
5-9 years	90	58.3	44.7-69.7	0			0.3	0.2-0.5

^a Only children born ≥37 weeks of gestation included. Information on gestational age was not available from the Northern Netherlands and their data are therefore excluded.

Figure 1. Percentage hospitalised for children with Pierre Robin sequence ('PRS'), children with any congenital anomaly ('Any CA') and children without a congenital anomaly ('Reference'), by age, 1995-2014

Table 4. Proportion of children with Pierre Robin sequence (n=261) undergoing surgery by age, 1995-2014

Age	N children undergoing surgery	% children undergoing surgery	95%CI
<1 year	174	67.6	46.6-81.8
1-4 years	147	61.1	43.6-74.7
0 to 4 years	205	99.2	94.4-99.9

* Data from Northern Netherlands were not available

Sup 1. Five-year survival estimates by registry (birth year period: 1995-2014)

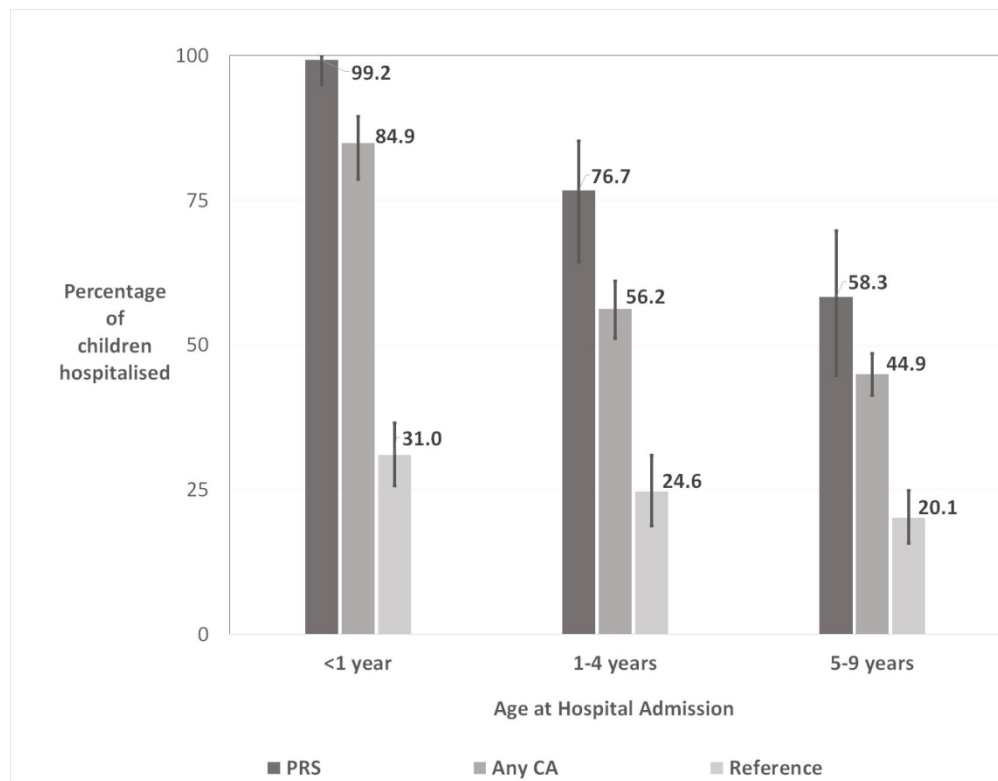
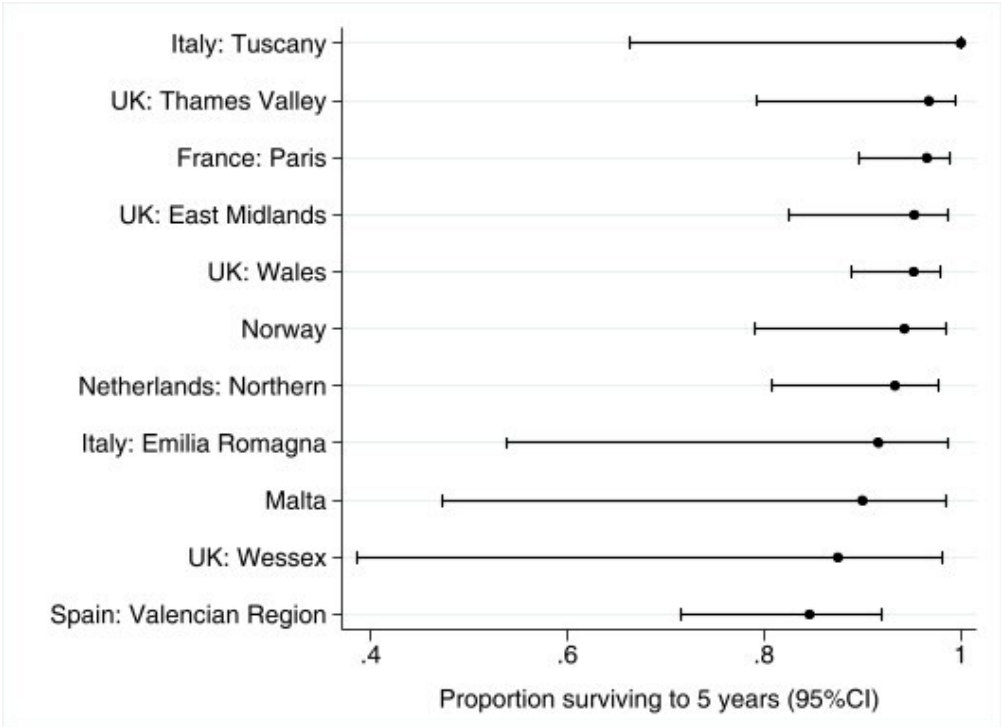


Figure 1. Percentage hospitalised for children with Pierre Robin sequence ('PRS'), children with any congenital anomaly ('Any CA') and children without a congenital anomaly ('Reference'), by age, 1995-2014

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44x32mm (300 x 300 DPI)