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DOI:

[10.1159/000480451](https://doi.org/10.1159/000480451)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Ali, K. A. M., Wijnen, R. M., & Tibboel, D. (2017). Congenital Diaphragmatic Hernia: 10-Year Evaluation of Survival, Extracorporeal Membrane Oxygenation, and Foetoscopic Endotracheal Occlusion in Four High-Volume Centres. *Neonatology*, 113, 63-68. <https://doi.org/10.1159/000480451>

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1 **Congenital diaphragmatic hernia; 10-year evaluation of survival, ECMO and FETO in 4 high-**  
2 **volume centres**

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20 **Key words:** congenital diaphragmatic hernia, extracorporeal membrane oxygenation, fetal intervention,  
21 mortality

22

23 **ABSTRACT**

24 **Background:** Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with significant  
25 mortality.

26 **Objectives:** To determine if there were trends in survival over the last decade and to compare patient  
27 populations, treatment options and survival rates between four high-volume centres and hence determine  
28 which factors were associated with survival.

29 **Methods:** In four high-volume CDH centres from the CDH EURO Consortium, data from all CDH patients  
30 born between 2004- 2013 were analysed. The predictive value of variables known at birth and the  
31 influence of centre-specific treatments (extracorporeal membrane oxygenation (ECMO) and fetoscopic  
32 tracheal occlusion (FETO)) on survival were evaluated in multivariable logistic regression analyses.

33 **Results:** Nine hundred and seventy-five patients were included in the analysis; 274 patients (28.1%)  
34 died. ECMO was performed in 259 patients of whom 81 (31.3%) died. One hundred and forty-five patients  
35 (14.9%) underwent FETO and from those 76 patients (52.4%) survived. Survival differed significantly  
36 between years ( $p=0.006$ ) and between the four centres ( $p<0.001$ ). In the multivariable logistic regression  
37 analysis, lung-to-head ratio, gestational age at birth, ECMO, centre of birth, and year of birth were  
38 significantly associated with survival, whereas FETO was not.

39 **Conclusions:** Patient populations were different between centres which influenced outcome. There was  
40 a significant variability in survival over time and between centres which should be taken into consideration  
41 in the planning of future trials.

42 **INTRODUCTION**

43 Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with a high variability of outcome  
44 [1]. Over the last decade new strategies have been introduced to evaluate and manage CDH patients. It  
45 is likely then that survival may have improved over that time, an aim of our study was to test that  
46 hypothesis.

47 Patient characteristics such as fetal liver position (intra-abdominal or intrathoracic) [2], stomach position  
48 [3], and lung-to-head ratio (LHR) [4]/ observed-to expected LHR [5] and the diaphragmatic defect size [6]  
49 can influence outcome as well as treatment in a high or low volume centre. There are differences in  
50 opinion about whether extracorporeal membrane oxygenation (ECMO) improves survival as no specific  
51 trials have been conducted with the primary aim of evaluating the role of ECMO specifically for high-risk  
52 CDH patients [7, 8]. The UK ECMO randomised trial investigated the role of ECMO for neonates, but only  
53 19% of those included had CDH and there was no significant difference in that subgroup with regard to  
54 survival [9]. In a multicentre, randomised, clinical trial (RCT) of initial ventilation strategy, in which centres  
55 with and without ECMO availability were included, no difference in survival between centres was  
56 observed [10]. Many CDH centres chose not to use ECMO because of the perceived poor outcome of  
57 CDH infants requiring ECMO [11]. Therefore, an important question is does ECMO influence survival? In  
58 the most severe, prenatally detected CDH cases, fetoscopic endotracheal occlusion (FETO) may improve  
59 outcome [12, 13]. To date, however, the results of only one small RCT have been reported. In an RCT of  
60 20 severe CDH patients of FETO versus postnatal management, survival was significantly better in the  
61 FETO group [14]. Thus, it is important to further determine the influence of FETO on survival while the  
62 results of the so called TOTAL trial are to be available in 2018. Analysing the results of four high-volume  
63 CDH centres our further aim, therefore, was to compare patient populations, treatment options and  
64 survival rates to determine which factors were associated with survival.

65 **PATIENTS AND METHODS**

66 An observational cohort study was performed of all patients with CDH who were born between January  
67 2004 and December 2013 and treated in four high-volume centres of the CDH EURO Consortium. The  
68 four centres were Rotterdam, London, Mannheim and Rome. Since 2008, all patients have been treated  
69 according to a standardized treatment protocol [15]. The standardized treatment included immediate  
70 intubation after birth, permissive hypercapnia, initial ventilation by high-frequency oscillation or

71 conventional mechanical ventilation, surgical repair of the defect after physiological stabilization, no  
72 routine chest tube placement, no routine use of paralysis. ECMO was only used routinely in some  
73 centres. In Rotterdam and Mannheim, ECMO therapy was available during the whole inclusion period, in  
74 Rome ECMO was available in 2013 only and in London infants could be transferred to an ECMO centre.  
75 FETO was available in the four centres on compassionate use.

76 ECMO criteria were an inability to maintain preductal saturations >85% or postductal saturations >70%; a  
77 high PaCO<sub>2</sub> with a respiratory acidosis (pH <7.15) despite optimization of ventilatory management (peak  
78 inspiratory pressure >28 cm H<sub>2</sub>O or mean airway pressure >17 cm H<sub>2</sub>O to achieve saturation >85%;  
79 inadequate oxygen delivery with a metabolic acidosis, lactate level >5 mmol/l and pH <7.15); systemic  
80 hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12–  
81 24 hours; oxygenation index (mean airway pressure x FiO<sub>2</sub> x 100/PaO<sub>2</sub>) ≥40. Before 2008, in Mannheim,  
82 ECMO criteria included an oxygenation index >35 for 0.5- 6 hours and a pH <7.25. In London, FETO  
83 therapy was only offered within the context of research trials (NCT01240057) from 2013 onwards and  
84 before 2010 as compassionate use. Inclusion criteria for FETO were: isolated left-sided CDH and severe  
85 pulmonary hypoplasia defined as observed-to-expected LHR <25% as measured prior to 29 weeks+ 6  
86 days, irrespective of the liver position.

87  
88 Patient demographics and management strategies, including prenatal diagnosis, LHR, FETO, gestational  
89 age, birth weight, gender, side of the defect, liver position (intrathoracic or intra-abdominal determined  
90 during surgical repair), type of repair (primary closure or patch repair), age at surgical repair, ECMO,  
91 ventilation days in survivors, inhaled nitric oxide (iNO) and survival were collected from the medical  
92 records. Death during the first year after birth was determined.

### 93 **Analysis**

94 To determine whether differences in the demographics of the infants in the four centres were statistically  
95 significant, chi-square tests for categorical data, or Kruskal-Wallis tests for continuous data were used.  
96 Mann-Whitney U tests for continuous data and chi-square tests for categorical data were applied to  
97 compare centre of birth and patient characteristics that were known at birth between survivors and non-  
98 survivors. In these univariate comparisons, year of birth was treated as a categorical variable.  
99 Associations between prenatal diagnosis, LHR, FETO, gestational age, gender, side of the defect,  
100 ECMO, centre and year of birth as independent variables and survival were determined using  
101 multivariable logistic regression analysis. The goodness-of-fit of the logistic regression model was  
102 assessed using the Hosmer-Lemeshow test. Analyses were performed using SPSS 22.0 for Windows  
103 (SPSS, Inc., Chicago, IL).

### 104 **RESULTS**

105 During the study period, there were 975 CDH patients; 274 (28.1%) patients died. A prenatal diagnosis  
106 was made in 820 (84.1%) patients. Overall, there was a significant difference in survival over the years  
107 ( $p=0.006$ ) (Figure 1). The survival rate differed from 29% to 97% over the years and centres.

108 Prenatal diagnosis, LHR, FETO, gestational age, birth weight, gender, liver position at surgical repair,  
109 type of repair, age at surgical repair, ECMO, ventilation days in survivors, use of iNO and survival were  
110 significantly different between the four centres (Table 1). Survivors significantly less often had a prenatal  
111 diagnosis, had higher LHRs and gestational ages and a greater proportion had a left-sided defect than  
112 non-survivors (Table 2).

113 There were also significant differences in survival regarding year of birth and centre of birth (Table 2). In  
114 Mannheim, 196 patients (41.8%) received ECMO and 153 (78.1%) of the ECMO-treated patients  
115 survived. In Rotterdam, 62 patients (31.8%) received ECMO and 25 (40.3%) of the ECMO-treated  
116 patients survived. ECMO treated patients in Rotterdam had lower LHRs and more often had a patch  
117 repair compared to the ECMO treated patients in Mannheim. In Rome, in 2013 one patient received  
118 ECMO and died. None of the patients from London received ECMO. ECMO use between survivors and  
119 non-survivors was not statistically significant. FETO was significantly more often used in non-survivors  
120 (25.2%) than in patients who survived (12.5%).

121 In the multivariable logistic regression analysis, a lower LHR, lower gestational age, ECMO, centre of  
122 birth and year of birth were significantly associated with death (Table 3). FETO was not significantly  
123 associated with death. The p-value of the Hosmer-Lemeshow test was larger than 0.05, indicating an  
124 adequate model calibration.

## 125 **DISCUSSION**

126 We have demonstrated variability in survival across a ten year period and between four high volume CDH  
127 centres. In addition, we highlight that the patient populations differed significantly between the centres  
128 and this influenced outcome. The survival rate was very different each year (Figure 1).

129 In the univariable analysis, we did not find a significant difference in ECMO use between survivors and  
130 non-survivors. In the multivariable analysis with correction for patient characteristics, however, we found  
131 that ECMO was significantly associated with death. This may be explained by the fact that only the most  
132 severe CDH cases receive ECMO. The frequency of use of ECMO and the outcomes was different  
133 between centres. In Mannheim 42% of the patients received ECMO and 78% of them survived, whereas  
134 in Rotterdam 32% of the patients received ECMO and only 41% of them survived. ECMO treated patients  
135 in Rotterdam, however, had lower LHRs and more often had a patch repair, suggesting they were in a  
136 more severe category. To identify for which subgroup of CDH patients ECMO might be most beneficial,  
137 predictive postnatal clinical models such as the Score for Neonatal Acute Physiology-II [16] or the clinical  
138 prediction score by Brindle et al [17] may be useful.

139 FETO was significantly more often used in non-survivors likely reflecting the selection criteria for  
140 compassionate use. Because FETO was only used on a compassionate basis, it precludes any  
141 meaningful conclusion with regards to the influence of FETO on survival. Hopefully, the TOTAL trial [18]  
142 will give a definitive answer to the benefit of FETO for patients with severe CDH.

143 High-volume CDH centres have more experience in treating CDH infants than low-volume centres and  
144 better outcomes [19]. Nevertheless, the patient characteristics were very different between the four high-  
145 volume centres and, despite correction for patient characteristics in the multivariable analysis, centre  
146 significantly influenced survival. This emphasizes the need for correction for centre in analyses of future  
147 multicentre studies on CDH.

148 Our study has many strengths and some limitations. We examined the outcome of a large sample  
149 (n=975) over ten years in four high-volume centres. Despite all centres during the study period had  
150 agreed use of a consistent protocol, we cannot rule out the possibility that differences in physicians,  
151 nursing staff and training may have influenced our results. This needs to be taken into account in future  
152 RCTs.

## 153 **CONCLUSION**

154 We have demonstrated variability in survival of CDH patients over time and between centres. Such  
155 differences need to be taken into account when planning future trials.

## 156 **ACKNOWLEDGEMENTS**

157 **Financial disclosure:** The authors have no financial relationships relevant to this article to disclose.

158 **Funding source:** No funding was received in support of this work.

159 **Potential conflicts of interest:** The authors have no conflicts of interest relevant to this article to  
160 disclose.

161 **Contributors' statement:** KGS conceptualized and designed the study, carried out the initial analyses  
162 and drafted the initial manuscript. AG, IC, TS, KA, RMW coordinated and supervised data collection and  
163 critically reviewed the manuscript. JVR carried out the initial analyses and reviewed and revised the  
164 manuscript. DT conceptualized and designed the study and critically reviewed the manuscript. All  
165 authors approved the final manuscript as submitted.

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226

227 **Figure 1. Survival of CDH by centre over the years**

228 **Figure 1**

229 \_\_\_\_\_ Rotterdam \_\_\_\_\_ London ----- Mannheim ----- Rome