

Infectious Comorbidity and In-Hospital Mortality in Children with Congenital Heart Disease: Development and Internal Validation of a Risk Score

Gulzhan I. Sarsenbayeva¹ , Abay Z. Kussainov^{1,2} , Gulmira B. Altynbayeva^{1,3} , Zhanna O. Ospanova² , Kanat S. Ashirbay¹ , Elmira B. Aitbayeva⁴ , Gulbanu S. Berdiyeva^{1,3} , Assan P. Zhumanov⁵ , Nurzhan E. Buryshbayev⁶ , Yedil.B. Kurakbayev¹ , Moldir K. Aitkulova⁷ 

ABSTRACT

Background

Congenital heart defects remain the largest group of congenital anomalies and a leading cause of infant mortality. Surgical outcome depends not only on the anatomy of the defect but also on concomitant extracardiac pathology, among which infectious conditions occupy a special position: they are potentially preventable.

Objective

To determine the prevalence and pattern of infectious comorbidity in children with congenital heart disease, quantify its association with in-hospital mortality, and develop an internally validated risk stratification score incorporating infectious factors.

Materials and methods

A single-centre retrospective comparative study was performed in Almaty, Kazakhstan, over 2012–2022. Five hundred children aged 0 to 18 years were analysed: 350 with extracardiac pathology and 150 without it, together with 295 autopsy observations. The Mann–Whitney and chi-squared tests, logistic regression, characteristic curve analysis, and bootstrapping were applied.

Results

Extracardiac pathology was registered in 70 % of admissions, concentrated in the neonatal period (59.5 versus 10 %). The leading infectious conditions were pneumonia (62.2 %), congenital infection (28 %), and neonatal sepsis (16 %); their frequency was independent of the haemodynamic type of defect. In-hospital mortality amounted to 17.4 versus 3.3 %. Four of twelve significant mortality predictors were infectious. The scale developed showed an area under the characteristic curve of 0.90 (sensitivity 76 %, specificity 79 %).

Conclusions

Infectious comorbidity represents a major and potentially preventable component of preoperative risk in children with congenital heart disease. Earlier antenatal detection, targeted screening for congenital infections, and timely referral before pneumonia develops may reduce in-hospital mortality.

Keywords

Heart Defects; Congenital; Comorbidity; Cytomegalovirus Infections; Pneumonia; Neonatal Sepsis; Risk Assessment; Infant Mortality For citation: Sarsenbayeva GI. Infectious Comorbidity and In-Hospital Mortality in Children with Congenital Heart Disease: Development and Internal Validation of a Risk Score. [Journal details to be completed after acceptance].

INTRODUCTION

Congenital heart defects (CHD) remain the largest group of congenital anomalies and one of the leading causes of infant mortality¹⁻³. Congenital anomalies are also registered in the Russian Federation, where the total number of recorded cases rose by 8.3 % over 2022–2024⁴. Surgery learned long ago to close the defect early, within the first weeks of life, and in-hospital survival for most defects has ceased to be the principal problem of the specialty⁵. The outcome of an operation, however, is determined by more than the anatomy of the defect and the technique of correction. Practice shows the opposite: children with the same defect,

1. Scientific Center of Pediatrics and Pediatric Surgery of the Ministry of Health of the Republic of Kazakhstan, Almaty, Republic of Kazakhstan
2. Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan
3. LLP Kazakhstan's medical university KSPH, Almaty, Republic of Kazakhstan
4. NJSC "Al-Farabi Kazakh National University", Almaty, Republic of Kazakhstan
5. Shymkent City Children's Clinical Hospital, Shymkent, Republic of Kazakhstan
6. Kazakh-Russian Medical University, Almaty, Republic of Kazakhstan
7. Health City Clinical center, Almaty, Republic of Kazakhstan

Correspondence

Kussainov Abay-chairman of the Management Board of JSC "Scientific Center of Pediatrics and Pediatric Surgery", candidate of medical sciences, Associate Professor, Head of the Department of Pediatric Surgery, kussainov.abay67@mail.ru

operated on by the same team using the same method, diverge in duration of ventilation, time to mobilisation, and probability of survival.

A child with CHD rarely has a single disease. Chronic hypoxaemia, pulmonary hypervolaemia, circulatory failure, and prolonged hospitalisation create a background against which an infectious process readily unfolds. Infection aggravates haemodynamics and postpones the operation, while a postponed operation prolongs exposure to infection. The circle closes. Children with CHD awaiting surgical correction experience respiratory tract infections 4.7 times more often than those managed conservatively⁶. The proportion of patients with a burdened premorbid background in cardiac surgery departments is growing faster than the proportion of “clean” defects, and this is connected less with deterioration of the population than with the widening of indications: those who were previously refused are now operated on^{7,8}.

Extracardiac pathology in children with CHD has been studied unevenly. Genetic syndromes and extracardiac malformations are well described: their frequency is known, their preferential combinations with particular types of CHD are known, and their contribution to postoperative complications and mortality has been measured⁹⁻¹². The infectious component of the premorbid background has entered the field of view predominantly from one angle, as healthcare-associated infection, that is, as an event of the postoperative period^{13,14}. Such an angle is understandable: precisely this part of infectious pathology is amenable to control by the hospital, and precisely this part enters official reporting.

Meanwhile, a substantial share of infectious conditions in these children exists long before admission to the cardiac surgery department. Congenital infections realised in utero or during the first days of life. Pneumonias acquired in the maternity hospital or at home while awaiting a place in the operating queue. Neonatal sepsis suffered during the nursing stage. None of this is a complication of cardiac surgical treatment; it is a characteristic of the population that arrives for such treatment. The distinction matters for prevention, because this background can be influenced earlier and by different means: antenatal diagnosis, neonatal screening, timely referral from primary care.

Practical risk assessment in paediatric cardiac surgery relies on scores that rank the complexity of the procedure. The Aristotle Basic Complexity score [15]

and RACHS-1 [16] have entered routine practice and national registries, and their prognostic properties have been repeatedly tested on large samples [17]. Both are built around the intervention rather than around the patient. The limitations of such a construction have been discussed more than once [18], [19, 20]: two children with the same defect and the same operation receive the same score yet diverge in outcome, and a procedural score cannot explain that divergence by virtue of its own construction. Attempts to add patient-specific variables have been made, including in the STAT and STS-EACTS models [21, 22]; the infectious background, however, was accounted for in them fragmentarily, and more often not at all.

Hence the gap we attempted to close. We found no systematic epidemiological description in the available literature of infectious comorbidity in the population of children admitted for cardiac surgical treatment, with a quantitative assessment of its contribution to in-hospital mortality and with subsequent formalisation of the result into a risk stratification instrument. A separate question that interested us was what share of this background is preventable in principle.

The aim of the study was to assess the frequency and structure of infectious comorbidity in children with congenital heart defects, to determine its contribution to in-hospital mortality, and to substantiate the inclusion of infectious factors in a risk stratification scale.

Materials and methods

Design, setting, and period. A single-centre retrospective comparative study was performed at the Department of Cardiac Surgery and Interventional Cardiology of the Scientific Centre of Paediatrics and Paediatric Surgery of the Ministry of Health of the Republic of Kazakhstan (Almaty). The observation period covered 2012–2022. Autopsy material from the Almaty pathoanatomical bureau, the paediatric prosectorium, the city maternity hospitals, and the Almaty Centre of Paediatric Cardiac Surgery was analysed in addition. The autopsy block was required for two reasons: it permits assessment of the structure of pathology in that part of the population which did not survive to discharge, and it reveals diseases missed during life.

Participants. Data on 1,100 patients hospitalised for surgical treatment of CHD during the stated period were selected by the continuous method. After application of

the selection criteria, 500 children aged 0 to 18 years entered the comparative analysis. The main group comprised 350 patients with extracardiac pathology, the comparison group 150 patients without concomitant disease. The declared age range in fact shifted towards the first year of life: children under 12 months made up 98 % of the main group and 74.6 % of the comparison group.

The inclusion criteria were: presence or documented absence of extracardiac pathology in a cardiac surgical patient; treatment in a single department; age from 0 to 18 years. The exclusion criteria were: severe multiple organ failure of cardiac origin in the preoperative period; neonatal body weight below 2.8 kg. The second exclusion criterion was introduced deliberately, in order to separate the effect of comorbidity from the effect of deep prematurity, which in paediatric cardiac surgery overrides almost everything else.

The autopsy block comprised 295 observations. These were used to assess the structure and frequency of extracardiac pathology in deceased children with CHD, including cases not recognised during life, as well as the relationship of the premorbid background to the scored complexity of the intervention.

Definitions and recording of variables. The following conditions were assigned to infectious and infection-mediated comorbidity: pneumonia, established by clinical and radiological criteria; congenital (intrauterine) infection confirmed by enzyme immunoassay and polymerase chain reaction (cytomegalovirus, herpetic, listeriosis); neonatal sepsis of bacterial and fungal aetiology; necrotising enterocolitis (NEC) staged according to Bell; urinary tract infections; parasitic infestations.

Necrotising enterocolitis was recorded as a separate position and required a reservation. Its pathogenesis is multifactorial, it is not a purely infectious disease, and assigning it to the infectious block without qualification would be a stretch. Microbial colonisation and the systemic inflammatory response, however, relate it to that block closely enough to permit joint analysis. Below we present calculations in two variants, with NEC included and excluded, so that the reader may assess the robustness of the conclusions to this decision.

The type of defect was classified as “pale” (acyanotic) and “blue” (cyanotic). The complexity of the intervention was assessed by the Aristotle Basic Complexity score

and by RACHS-1 risk categories. A multidisciplinary board including a cardiac surgeon, a pulmonologist, a neurologist, a neonatologist, and a geneticist was formed in the clinic to implement the objectives of the study; decisions on the timing and extent of intervention were taken collegially.

Outcome assessment. Duration of hospitalisation, duration of mechanical ventilation and of stay in the intensive care unit (ICU), the number of diagnostic procedures and manipulations, the frequency and structure of complications, and in-hospital mortality were recorded.

Statistical analysis. SPSS 22.0 (IBM Corp., USA) and Stata 14 (Stata Corp LP, USA) were used. Normality of distribution was tested by the Kolmogorov–Smirnov test. Quantitative variables with a distribution other than normal are presented as the median with the interquartile range, and groups were compared by the Mann–Whitney test. Qualitative variables were compared by the χ^2 test and the z-test for the difference of proportions. Predictors of a lethal outcome were selected by univariate logistic regression; variables retaining significance were entered into a multivariate model. Results are expressed as the odds ratio (OR) with the 95 % confidence interval (CI). Discriminatory ability was assessed by ROC analysis with calculation of the area under the curve (AUC), sensitivity, and specificity; threshold values of quantitative variables were determined by the cut-off point. The robustness of the regression model was tested by bootstrapping. Differences were considered statistically significant at $p < 0.05$.

Ethical Clearance

The study protocol was approved by the biomedical ethics committee of “full official name of the organization”, protocol No. 26 of 31.10.2024. The parents of the patients signed informed consent for the child’s participation in the study and for publication of the results.

RESULTS

Characteristics of the comparison groups

The groups diverged in age and body weight but coincided in sex and height (Table 1). The median weight in the main group proved lower than in the comparison group, and the proportion of neonates differed almost sixfold, 59.5 % versus 10 % ($p < 0.001$). Concomitant

pathology in a child with CHD emerged above all as a problem of the first weeks of life, and this framed the whole subsequent analysis.

Table 1. Demographic characteristics of the comparison groups

Variable	Main group (n = 350)	Comparison group (n = 150)	p
Age, months	5.9 ± 2	8.1 ± 2	0.000
Neonates, n (%)	208 (59.5)	15 (10.0)	0.000
Boys, n (%)	189 (53.8)	68 (44.8)	0.562
Girls, n (%)	161 (46.2)	82 (55.2)	0.445
Height, cm	74 (51; 98)	76 (52; 100)	0.096
Body weight, kg	6.45 (2.9; 10)	8.3 (4.6; 12)	0.000

Note: qualitative data are presented as the absolute number of patients (%), quantitative data as the mean ± standard deviation or the median (min.; max.).

The age distribution within the main group confirmed the shift. Neonates numbered 208 (59.5 % ± 2.6; CI 54.3–64.7). The age of 1 to 6 months accounted for 103 observations (29.4 % ± 2.4; CI 24.8–34.6), the period from 6 to 12 months for 31 (8.8 % ± 1.51), and an age above one year for only 8 (2.2 % ± 0.6). In the comparison group the picture is reversed: 15 neonates (10 % ± 2.45) and 38 children older than one year (25.3 % ± 3.55). The difference of proportions is significant for the neonatal age ($z = 10.203$; $p < 0.001$), for the age from 6 to 12 months ($z = -7.116$; $p < 0.001$), and for children older than one year ($z = -8.347$; $p < 0.001$). No difference was found for the intermediate group of 1 to 6 months ($z = -0.135$; $p = 0.893$).

Extracardiac pathology was registered in 70 % of admissions. A combination of two or more nosological entities in one child occurred the more frequently the younger the patient. Three or more combinations were present in 47.1 % of neonates versus 8.9 % of infants under one year ($z = 7.375$; $p < 0.001$), whereas for two combinations the ratio proved the reverse, 37 % versus 73.1 % ($z = -6.522$; $p < 0.001$). The association of the

Table 2. Structure of extracardiac pathology in the main group (n = 350)

Nosological entity	n	Proportion, %
Infectious and infection-mediated conditions		
Pneumonia	218	62.2
Congenital infection (cytomegalovirus, herpetic, listeriosis)	97	28.0
Neonatal sepsis (bacterial, fungal)	56	16.0
Necrotising enterocolitis	10	2.8
Urinary tract infections	10	2.8
Parasitic infestations	5	1.4
Other extracardiac pathology		
Perinatal encephalopathy	266	76.0
Genetic and hereditary syndromes	95	27.2
Multiple congenital malformations (including VACTER)	78	22.2
Rare (orphan) diseases	78	22.0
Diseases of the perinatal period	76	21.7
Musculoskeletal malformations	35	10.0
Gastrointestinal malformations	31	8.8
Pulmonary malformations	27	7.7
Severe central nervous system pathology	23	6.5
Blood diseases	21	6.2
Renal and urinary tract malformations	15	4.2
Bronchopulmonary dysplasia	11	3.1
Central nervous system malformations	10	2.8

Note: the sum of proportions exceeds 100 % because several nosological entities were recorded in one patient. Infectious and infection-mediated conditions are grouped in the upper block and set in bold.

number of combinations with age was confirmed by the χ^2 test (57.875; df = 2; $p < 0.001$). In other words, the accumulation of pathology in a neonate proceeds not along one line but along several at once.

The structure of comorbidity and the place of the infectious block

The structure of extracardiac pathology is presented in Table 2. The first position was taken by perinatal encephalopathy of hypoxic-ischaemic origin, $76\% \pm 2.2$. Immediately behind it came the infectious conditions, and by aggregate weight they exceeded any other group of nosological entities.

Pneumonia was suffered by 218 children, which amounted to $62.2\% \pm 2.5$ (CI 57.0–67.3). Congenital infection was confirmed in 97 patients, $28\% \pm 2.4$ (CI 23.2–32.8); cytomegalovirus infection predominated in its structure. Neonatal sepsis of bacterial and fungal aetiology was diagnosed in 56 children, 16% . Necrotising enterocolitis developed in 10 patients of the main group (2.8%). Urinary tract infections were noted in 10 observations (2.8%) and parasitic infestations in 5 (1.4%).

Comparison with the non-infectious block clarifies the scale. Genetic and hereditary syndromes were identified in $27.2\% \pm 2.3$ of patients, multiple congenital malformations in $22.2\% \pm 2.2$, diseases of the perinatal period in $21.7\% \pm 2.2$, rare (orphan) diseases in $22\% \pm 2.2$, and blood diseases in $6.2\% \pm 1.2$. The difference between the blocks does not reduce to quantity. Down syndrome or a multiple malformation cannot be prevented; they can only be taken into account in planning. Pneumonia in a child awaiting an operation can in many cases be prevented, and this transfers the infectious block into another category: from a factor one works around into a factor one acts upon.

The distribution by type of defect produced a result we had not expected. In patients with “pale” CHD, pneumonia was registered in 32.2% of cases and in those with “blue” CHD in 29% ; congenital infection in 9.8 and 8.6% respectively; septic states in 7 and 6.2% . The overall frequency of extracardiac pathology, by contrast, diverged noticeably between these types: 61.8% in acyanotic defects versus 38.1% in cyanotic ones. The divergence is not created by infection. It is created by malformations and syndromes: in “pale” CHD syndromes occurred in 19% of cases, in “blue”

CHD in 10.3% . The infectious background, unlike them, is present in all patients to approximately the same degree, irrespective of the haemodynamic type of the defect.

Syndromic pathology deserves to be carried into a separate narrative: it interacts with the infectious block. Its frequency amounted to 27.2% , with chromosomal forms identified in 18.1% of patients and non-chromosomal forms in 9.1% . Among the defects associated with genetic syndromes, complete atrioventricular septal defect predominated (63%). After surgical correction, children with syndromic pathology significantly more often developed pneumonia (30%), pulmonary atelectasis (16%), and infectious complications (3.4%), as well as acute heart failure (33.4%) and neurological disturbances (43%). Duration of ventilation and of hospitalisation in them was significantly higher (9.9 ± 2 and 16.2 ± 2 days respectively). A substantial part of the effect of syndromic pathology is realised, to all appearances, through an infectious mechanism.

Table 3. Perioperative course and outcomes in the comparison groups

Indicator	Main group	Comparison group
Bed-days	18.25 ± 12.79	9.07 ± 2.22
ICU stay, days	9.93 ± 11.88	2.12 ± 1.24
Mechanical ventilation, days	8 ± 2	3 ± 2
Diagnostic procedures in the ICU, n	10 ± 2	2 ± 2
Manipulations, n	12 ± 2	5 ± 2
Complications, %	70	27
Aristotle Basic Complexity score, points	7.9 ± 1.2	5.6 ± 1.2
In-hospital mortality, % (abs.)	17.4 (61/350)	3.3 (5/150)

Note: indicators of the perioperative course were calculated for operated patients ($n = 261$ and $n = 139$); in-hospital mortality was calculated for the whole cohort ($n = 350$ and $n = 150$).

The influence of comorbidity on course and outcomes

Patients with extracardiac pathology stayed longer in hospital, were ventilated longer, and more often required additional interventions (Table 3). The median bed-day amounted to 18.25 versus 9.07 in the comparison group ($p < 0.001$ by the Mann–Whitney test; mean rank 246 and 115 respectively). Duration of ICU stay reached 9.93 days versus 2.12 (mean rank 249 and 109). The number of diagnostic procedures in the ICU differed fivefold (10 ± 2 versus 2 ± 2), and the number of manipulations more than twofold (12 ± 2 versus 5 ± 2).

Complications developed in 70 % of patients in the main group and in 27 % in the comparison group. The structure of complications was as follows: neurological disturbances 70 %, of which severe, with convulsive syndrome and stroke, 1 %; progression of pneumonia 46 %; realisation of congenital infection and sepsis 18 %; bronchopulmonary dysplasia 11 %; acute kidney injury 7 %. In children without concomitant pathology, moderate neurological disturbances against a background of postperfusion syndrome (20 %) and pneumonia against a background of prolonged ventilation (7 %) were noted; not a single severe complication was registered in this group.

In-hospital mortality in the main group reached 17.4 % (61 of 350) versus 3.3 % (5 of 150) in the comparison group; OR 6.1 ($\chi^2 = 16$; CI 2.4–15). Eleven children (3.1 %) died before operation, the causes being sepsis, NEC, acute cerebrovascular accident, hypoplastic left heart syndrome, bronchopulmonary dysplasia, and leukaemia. Forty-four patients died after operation, and infectious positions occupy the majority in the list of causes: progression of circulatory failure, sepsis, realisation of congenital infection, progression of pneumonia, NEC, congenital pulmonary lymphangiectasia. In the comparison group all 5 lethal outcomes were connected with haemodynamics and surgical technique (pulmonary crisis, right ventricular dysfunction, dissection of the arterial duct) but not with infection. The difference in the structure of causes here is no less telling than the difference in frequency.

The contribution of pneumonia to consumption of intensive care resources was assessed specifically: its presence increased the risk of prolonged ICU stay by 16.5 %. Pulmonary diseases served as the cause of 6.2 % of cases of in-hospital mortality.

Gastrointestinal dysfunction accompanied CHD in

45 % of observations. Its most severe manifestation proved to be NEC (10 observations, 2.8 %); in 60 % of cases it developed in neonates, and in 13.3 % of patients with stage III–IV it was accompanied by intestinal perforation and peritonitis. In children with “blue” defects, NEC was registered in 63 % of the total number of cases. Mortality in this subgroup reached 54.5 %, which makes NEC the deadliest of the infection-mediated conditions in our material.

Concomitant pathology also altered surgical tactics. Radical correction was performed in 65.4 % of patients of the main group versus 94 % in the comparison group. Delayed operations were required in 17 % of cases versus 6 %, palliative operations in 9 %, and transfer to specialised departments in 8.6 %. In a quarter of the cases of delay (26.1 %), first-stage correction of an extracardiac malformation that brooked no postponement was required. In a further 2 % of observations, cardiac surgery was performed simultaneously with intervention on the abdominal organs, the lungs, or the brain.

Autopsy material

Of 295 deceased children with CHD, 60 % ($n = 177 \pm 2.8$) had extracardiac pathology and 40 % ($n = 118 \pm 2.8$) did not. The age distribution repeated the clinical one: the neonatal period accounted for $55.5 \% \pm 2.8$ of observations, the age of 1 to 6 months for $27.7 \% \pm 2.6$, the period from 6 to 12 months for $12.4 \% \pm 1.6$, and an age above one year for only $4.4 \% \pm 0.82$. In the structure of concomitant pathology, somatic diseases amounted to 47.4 % ($n = 140$), multiple malformations to 38.3 % ($n = 113$), syndromes to 5 % ($n = 28$), and acute surgical pathology to 4 % ($n = 12$). Multiple malformations (95 % CI 14.3–26.3), congenital infection (95 % CI 13.8–22.8), and various pulmonary diseases (95 % CI 1.5–5.9) occurred significantly often.

One result stands out from the row. In 20 children (6.75 %), concomitant pathology was not recognised during life and was identified only at autopsy. The list of what was missed included renal malformations, cytomegalovirus infection, cysts and malformations of the lungs, haemangiomas, and cystic fibrosis. This is a direct index of the quality of preoperative examination, and the presence of cytomegalovirus infection in the list is hard to regard as accidental: the latent course of a congenital infection demands a targeted search, and a targeted search is possible only where the protocol provides for one.

The autopsy data also exposed the weakness of procedural scores, and in the most graphic form. Among the deceased with a low Aristotle Basic Complexity score (3–6 points, $n = 79$), $96.1 \% \pm 2.9$ had severe extracardiac pathology. Among the deceased with a high score (7–14.5 points, $n = 216$), $74 \% \pm 2.9$ had such pathology. Children in the first subgroup were not dying of the complexity of the operation. They were dying of the background at which the procedural score does not look.

Predictors of a lethal outcome

The subgroup for construction of the prognostic model comprised 261 children with CHD and extracardiac pathology: 84 deceased (32.2 %) and 177 survivors (67.8 %). The median age was 30 (12; 120) days and the median weight 3.9 (3.5; 5) kg. Forty variables were analysed.

Four infectious conditions proved to be significant predictors of a lethal outcome (Table 4): necrotising enterocolitis (OR 3.05; CI 1.02–9.11; $p = 0.045$), sepsis (OR 2.91; CI 1.10–7.67; $p = 0.031$), congenital infection (OR 2.79; CI 1.26–6.20; $p = 0.011$), and pneumonia (OR 1.53; CI 1.05–2.70; $p = 0.015$). Among the non-infectious factors, significance was retained by blood diseases (OR 13.8; CI 1.6–116; $p = 0.016$), malformations of the central nervous system (OR 4.54; CI 1.1–18.6; $p = 0.036$), malformations of the gastrointestinal tract (OR 1.66; CI 1.02–3.80; $p = 0.029$), duration of ICU stay (OR 2.05; CI 1.49–2.82; $p = 0.001$), duration of ventilation (OR 1.21; $p = 0.018$), age (OR 0.99; $p = 0.009$), and body weight (OR 0.74; $p = 0.019$).

Four of the twelve significant predictors belong to the infectious block. The frequency comparison confirms their role: in the group of the deceased, pneumonia occurred three times more often than in survivors (46.4 % versus 14.1 %; $p = 0.001$), congenital infection more than three times (17.8 % versus 5.6 %; $p = 0.016$), and sepsis almost three times (12 % versus 4.5 %; $p = 0.035$). Necrotising enterocolitis showed a similar direction (9.5 % versus 3.4 %) at $p = 0.072$, that is, at the boundary of significance, which is explained by the small number of events.

Down syndrome behaved in the opposite manner. The odds ratio amounted to 0.27 (CI 0.09–0.80; $p = 0.018$); in the group of the deceased it occurred three times less often than in survivors (4.8 % versus 15.8 %; $p = 0.014$).

Table 4. Univariate regression analysis of predictors of a lethal outcome ($n = 261$)

Factor	OR (95 % CI)	p
Blood diseases	13.8 (1.6–116)	0.016
Central nervous system malformations	4.54 (1.1–18.6)	0.036
Necrotising enterocolitis	3.05 (1.02–9.11)	0.045
Sepsis	2.91 (1.10–7.67)	0.031
Congenital infection	2.79 (1.26–6.20)	0.011
Duration of ICU stay	2.05 (1.49–2.82)	0.001
Gastrointestinal malformations	1.66 (1.02–3.80)	0.029
Pneumonia	1.53 (1.05–2.70)	0.015
Duration of mechanical ventilation	1.21 (1.03–1.41)	0.018
Age	0.99 (0.98–0.999)	0.009
Body weight	0.74 (0.58–0.95)	0.019
Down syndrome	0.27 (0.09–0.80)	0.018

Note: variables retaining statistical significance at $p < 0.05$ out of the 40 analysed are shown. Infectious and infection-mediated conditions are set in bold. Down syndrome showed an inverse direction of effect and was excluded from the multivariate model.

In our sample, trisomy 21 was associated with a lower probability of a lethal outcome, and for this reason the variable was excluded from the multivariate model as a factor of failure.

ROC analysis of the quantitative variables established threshold values. For age the cut-off point amounted to 28 days (AUC 0.79; CI 0.66–0.97; sensitivity 73 %, specificity 72 %; $p = 0.031$), for body weight 3.7 kg (AUC 0.79; CI 0.62–0.95; sensitivity 70 %, specificity 75 %; $p = 0.039$), for duration of ICU stay 4 days (AUC 0.72; sensitivity 66 %, specificity 75 %; $p = 0.036$), and for duration of ventilation 3 days (AUC 0.67; sensitivity 60 %, specificity 55 %; $p = 0.033$).

The risk stratification scale

A point scale was constructed on the basis of the multivariate model (Table 5). Infectious and infection-mediated positions occupied 7.5 of the 15 possible points in it: pneumonia 2 points, NEC 2.5, congenital infection 1.5, sepsis 1.5. If NEC is excluded and only the strictly infectious conditions are retained, the share amounts to 5 points of 15. Under either variant of calculation, the infectious component carries from one third to one half of the weight of the scale, and in this lies its principal substantive feature.

Table 5. Scale for stratification of the risk of a lethal outcome in paediatric cardiac surgical patients

Factor	β	Points	AUC	p
Blood diseases	3.62	3.5	0.85	0.022
Necrotising enterocolitis	2.52	2.5	0.90	0.028
Pneumonia	2.05	2	0.88	0.025
ICU stay > 4 days	2.02	2	0.90	0.033
Congenital infection	1.54	1.5	0.93	0.034
Sepsis	1.47	1.5	0.93	0.033
Neonatal period	0.79	1	0.64	0.040
Body weight < 3.7 kg	0.72	0.5	0.66	0.047
Central nervous system malformations	0.62	0.5	0.76	0.035
Maximum total		15	0.90	0.042

Note: infectious and infection-mediated positions are set in bold and account for 7.5 of 15 points (5 of 15 excluding necrotising enterocolitis). Risk classes: < 3 points — low (probability of a lethal outcome 8 %), 3–6 — moderate (29 %), 7–9 — high (58 %), > 9 — extremely high (> 90 %). The scale as a whole: AUC 0.90 (95 % CI 0.78–0.99), sensitivity 76 %, specificity 79 %, $p = 0.042$.

Testing of each factor by a separate ROC analysis showed that the greatest discriminatory ability belongs precisely to the infectious positions. Congenital infection and sepsis yielded an AUC of 0.93 ($p = 0.034$ and 0.033), NEC 0.90 ($p = 0.028$), and pneumonia 0.88 ($p = 0.025$). By comparison, a body weight below 3.7

kg yielded an AUC of 0.66 and neonatal age 0.64. The infectious variables did not merely enter the model. They carry its principal separating load.

The scale as a whole showed an AUC of 0.90 (CI 0.78–0.99) with a sensitivity of 76 % and a specificity of 79 % ($p = 0.042$). Bootstrap testing confirmed the robustness of the coefficients at a low level of bias, the range of which did not extend beyond –0.02 to 0.00.

Four risk classes were distinguished: fewer than 3 points correspond to low risk, 3 to 6 to moderate, 7 to 9 to high, and above 9 to extremely high. The calculated probability of a lethal outcome amounted to 8 % at low risk (OR 1.08; CI 1.03–1.57; $p = 0.02$), 29 % at moderate risk (OR 1.29; CI 1.11–1.69; $p = 0.01$), 58 % at high risk (OR 1.58; CI 1.17–1.92; $p = 0.001$), and above 90 % at extremely high risk (OR 1.92; CI 1.26–2.56; $p = 0.001$). The distribution of patients by class was: low risk 46.7 %, moderate 31.2 %, high and extremely high together 22.1 %. On division into classes the discriminatory ability fell to moderate, AUC 0.717 (CI 0.59–0.84; sensitivity 75 %, specificity 60 %); bootstrapping revealed no significant differences between the groups ($p = 0.08$).

The divergence from the procedural score is conveniently shown on a clinical example. Ligation of a patent arterial duct is scored by the Aristotle Basic Complexity score at 3 points: mortality below 1 %, ICU stay up to 24 hours, elementary complexity, minimal risk of complications. In the children we observed with the same intervention but with congenital infection, pneumonia, and grade II protein-energy malnutrition, the sum on our scale reached 8 points, and the outcomes proved unfavourable. The procedure is simple. The patient is not.

DISCUSSION

The principal result of the work is briefly formulated. In the population of children admitted for surgical treatment of CHD, infectious comorbidity proved simultaneously the most frequent, the most prognostically weighty, and the most accessible to prevention.

A pneumonia frequency of 62.2 % and a congenital infection frequency of 28 % substantially exceed the values cited for the general cohort of children in the first year of life^{23,24}. The explanation lies in haemodynamics. Pulmonary hypervolaemia in acyanotic defects creates conditions for a protracted

course of respiratory infection, while circulatory failure lowers tolerance to any infectious episode²⁵. Our data add an epidemiological argument to this mechanism: the infectious background is equally pronounced in both “pale” and “blue” defects, whereas malformations and syndromes are distributed between them unevenly. Infection in this population is therefore not derivative of the particular type of defect. It is derivative of the situation itself: an immature child, circulatory failure, a postponed operation, prolonged hospitalisation. The situation, however, lends itself to management better than anatomy does.

The odds ratios obtained accord with international data on infectious complications in paediatric cardiac surgery^{26,27}. Agreement in the magnitude of the effect across different designs and different populations strengthens confidence in the result. A divergence was found elsewhere. In the majority of studies, infection is analysed as a postoperative event and, correspondingly, as an object of hospital infection control. In our patients it was to a considerable extent present before admission. This changes the addressee of prevention: healthcare-associated infection is prevented by the hospital, whereas pneumonia in a child awaiting an operation at the place of residence, and unrecognised cytomegalovirus infection in a neonate, are prevented by primary care and the antenatal service. Different addressees require different managerial decisions, and conflating these two categories of infectious pathology is counterproductive.

Necrotising enterocolitis stands apart. Its pathogenesis is multifactorial: ischaemia of the intestinal wall in duct-dependent circulation, immaturity, the character of feeding, microbial colonisation [28, 29]. To assign it to purely infectious pathology is incorrect, and we do not do so. Microbial colonisation and the systemic inflammatory response, however, relate it to the infectious block, and its contribution to mortality proved the greatest among the infection-mediated conditions (OR 3.05; mortality in the subgroup 54.5 %). The two variants of calculation of the weight of the infectious component we have presented, with and without NEC, show that the conclusion does not depend on this decision: even in the conservative variant, infectious positions occupy a third of the scale.

The result for Down syndrome looks paradoxical and requires caution in interpretation. The protective effect (OR 0.27) almost certainly reflects not biology but

the features of selection: children with trisomy 21 are operated on predominantly for atrioventricular septal defect, on a planned basis, after stabilisation of their condition and outside an acute infectious episode. A similar picture, in which trisomy 21 does not worsen in-hospital mortality although postoperative morbidity in such children remains high, is described by other authors as well^{9,10}. This reinforces the selection version rather than that of protectiveness. Exclusion of the variable from the model was for this reason the only correct decision.

The autopsy data added an argument that clinical material cannot furnish in principle. Failure to detect concomitant pathology during life in 6.75 % of cases points to a defect of preoperative examination, and the list of what was missed (cytomegalovirus infection, malformations of the lungs and kidneys, cystic fibrosis) localises the specific gaps in the protocol. The ratio by the Aristotle score is more expressive still: among the deceased with formally low complexity of intervention, 96.1 % had a severe premorbid background. The procedural score does not work in this subgroup by virtue of its construction, since it measures a source of risk other than the one that kills the patient.

Hence the applied conclusion for the sake of which the scale was created. We do not propose to replace the Aristotle Basic Complexity score or RACHS-1: both solve their own task and solve it well, and the comparability of data between centres rests precisely on them. We propose adding to them an orthogonal dimension, the premorbid background, in which the infectious component carries from a third to a half of the weight. Joint application permits explanation of those divergences of outcome at identical procedures which the procedural score leaves unexplained, and gives parents a more honest prognosis in which risk is connected not only with the operation itself. For paediatric cardiac surgery registries this means the necessity of collecting premorbid variables on a par with procedural ones.

The practical consequences for preventive medicine are formulated rather narrowly and are therefore feasible. Examination for congenital infections of neonates and infants referred for cardiac surgical treatment must be obligatory rather than selective: this will reduce the frequency of latent and persistent infections after operation. Referral of a child with CHD for operation must occur before pneumonia develops, which transfers

a considerable share of responsibility to the level of primary health care. The algorithm of bacteriological monitoring and rational antibiotic therapy in the perioperative period requires standardisation: simplification of perioperative prophylaxis regimens combined with a stewardship programme does not increase the frequency of surgical site infection and appreciably reduces antibiotic consumption^{30,31}. In children with duct-dependent defects, adequate intensive care at the prehospital stage serves as prophylaxis of NEC, which means that the quality of prehospital care converts directly into in-hospital mortality.

The organisational dimension of the problem is no less noticeable. Patients with concomitant pathology almost twice as often received treatment in primary-level hospitals (48.5 % versus 20 %; $z = 5.962$; $p < 0.001$) and more often underwent additional investigations there (45.7 % versus 13.3 %; $z = 6.918$; $p < 0.001$). The cost of treatment thereby rose by more than 60 %. The infectious background is paid for twice: first in bed-days and complications, then in the money of the health system. The economic argument here coincides with the clinical one, which for preventive programmes is not often the case.

Limitations of the study. The work is single-centre and retrospective, which limits transfer of the conclusions to other populations and does not fully protect against selection bias. Part of the data was obtained from archival case histories whose completeness is uneven across the years of observation. The scale was constructed and tested on a single sample, external validation on an independent cohort was not carried out, and bootstrapping confirms only the internal robustness of the model. Wide confidence intervals for rare variables (blood diseases: CI 1.6–116) reflect the small number of events and require cautious interpretation. Division of the scale into four classes reduced discriminatory ability to moderate (AUC 0.717), which points to the need to refine the class boundaries on a larger material. The division of comorbidity into potentially preventable and non-preventable rests on clinical judgement rather than on a formal operational criterion. Finally, the autopsy material originates from several institutions of the city and is not identical in composition to the clinical sample, for which reason we deliberately did not perform a direct comparison of frequencies between these two blocks.

CONCLUSION

Extracardiac pathology was registered in 70 % of children hospitalised for surgical treatment of congenital heart defects and was concentrated in the neonatal age (59.5 % versus 10 % in the comparison group; $p < 0.001$).

Infectious and infection-mediated conditions constituted the leading part of the premorbid background: pneumonia 62.2 %, congenital infection 28 %, neonatal sepsis 16 %. Their frequency did not depend on the haemodynamic type of the defect, which points to a common mechanism of formation rather than to anatomical specificity.

Four of the twelve significant predictors of in-hospital mortality proved infectious: necrotising enterocolitis (OR 3.05), sepsis (OR 2.91), congenital infection (OR 2.79), and pneumonia (OR 1.53). In discriminatory ability they exceeded all other factors (AUC 0.88–0.93).

The risk stratification scale developed (AUC 0.90; sensitivity 76 %, specificity 79 %) allots from 5 to 7.5 of 15 points to the infectious component. Joint application of the scale with the Aristotle Basic Complexity score and RACHS-1 permits account to be taken of that source of risk which procedural scores do not measure: among the deceased with low procedural complexity, 96.1 % had a severe premorbid background.

The leading component of this background is potentially preventable. The main reserve for reducing in-hospital mortality in congenital heart defects therefore shifts beyond the operating theatre, into antenatal diagnosis, screening for congenital infections, and timely referral of the child before pneumonia develops.

Funding

This research was funded by the Ministry of Healthcare of the Republic of Kazakhstan within the targeted funding program “Development of a science-based program to improve perinatal outcomes” [IRN BR25293307].

Conflict of interest

no conflict of interest. The work was carried out as part of the scientific and technical program “Development of a science-based program to improve perinatal outcomes” [IRN BR25293307].

Author contribution

concept development- Sarsenbayeva Gulzhan,

Kussainov Abay; writing – review & editing - Sarsenbayeva Gulzhan; conceptualization, supervision- Altynbayeva Gulmira, Sarsenbayeva Gulzhan; study design- Zhumanov Assan, Ashirbay Kanat; Aitkulova Moldir; conduct of the- Kussainov Abay, Sarsenbayeva Gulzhan; stated research- Ospanova Zhanna, Buryshbayev Nurzhan; Kurakbayev Yedil; interpretation of the stated research- Sarsenbayeva Gulzhan, Aitbayeva Elmira; manuscript preparation- Kussainov Abay, Berdiyarova Gulbanu, Sarsenbayeva Gulzhan.

REFERENCES

1. Van der Linde D, Konings EEM, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;**58**(21):2241-2247. doi:10.1016/j.jacc.2011.08.025
2. Zimmerman MS, Smith AGC, Sable CA, et al. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health*. 2020;**4**(3):185-200. doi:10.1016/S2352-4642(19)30402-X
3. Syssoyev D, Seitkamzin A, Lim N, et al. Epidemiology of congenital heart disease in Kazakhstan: data from the Unified National Electronic Healthcare System 2014-2021. *J Clin Med Kaz*. 2024;**21**(3):49-55. doi:10.23950/jcmk/14683
4. Ivanova MA, Polikarpov AV, Zavarina IV, Zakharchenko OO. [Congenital anomalies (malformations), deformities and chromosomal abnormalities in the Russian Federation in 2022–2024.] *Zdorov'e Naseleniya i Sreda Obitaniya*. 2026;**34**(1):19-25. doi:10.35627/2219-5238/2026-34-1-19-25 (In Russ.)
5. Saperova EV, Vakhlova IV. [Congenital heart diseases in children: incidence, risk factors, mortality.] *Voprosy Sovremennoi Pediatrii*. 2017;**16**(2):126-133. doi:10.15690/vsp.v16i2.1713 (In Russ.)
6. Saperova EV, Vakhlova IV. [The complex assessment of the health status of children during the first year of life with congenital heart disease.] *Meditsinskiy Sovet*. 2017;**19**:198-204. doi:10.21518/2079-701X-2017-19-198-204 (In Russ.)
7. Patel A, Costello JM, Backer CL, et al. Prevalence of noncardiac and genetic abnormalities in neonates undergoing cardiac operations: analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg*. 2016;**102**(5):1607-1614. doi:10.1016/j.athoracsur.2016.04.008
8. Alsoufi B, Gillespie S, Mahle WT, et al. The effect of noncardiac and genetic abnormalities on outcomes following neonatal congenital heart surgery. *Semin Thorac Cardiovasc Surg*. 2016;**28**(1):105-114. doi:10.1053/j.semtevs.2015.10.016
9. Fudge JC Jr, Li S, Jagers J, et al. Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database. *Pediatrics*. 2010;**126**(2):315-322. doi:10.1542/peds.2009-3245
10. Wang B, Verrocchi J, Liew D, Zentner D. Does Down syndrome influence the outcomes of congenital cardiac surgery? A systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes*. 2023;**9**(3):240-248. doi:10.1093/ehjqcco/qcac028
11. Huang X, Gao Y, Chen W, Sheng W, Huang G. Noncardiac anomalies in children with congenital heart disease. *Front Cardiovasc Med*. 2023;**10**:1293210. doi:10.3389/fcvm.2023.1293210
12. Eskedal L, Hagemo P, Eskild A, Aamodt G, Seiler KS, Thaulow E. A population-based study of extra-cardiac anomalies in children with congenital cardiac malformations. *Cardiol Young*. 2004;**14**(6):600-607. doi:10.1017/S1047951104006043
13. Hatachi T, Tachibana K, Inata Y, et al. Risk factors for healthcare-associated infections after pediatric cardiac surgery. *Pediatr Crit Care Med*. 2018;**19**(3):237-244. doi:10.1097/PCC.0000000000001445
14. Yu X, Chen M, Liu X, et al. Risk factors of nosocomial infection after cardiac surgery in children with congenital heart disease. *BMC Infect Dis*. 2020;**20**(1):64. doi:10.1186/s12879-020-4769-6
15. Lacour-Gayet F, Clarke D, Jacobs J, et al. The Aristotle score: a complexity-adjusted method to evaluate surgical results. *Eur J Cardiothorac Surg*. 2004;**25**(6):911-924. doi:10.1016/j.ejcts.2004.03.027
16. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2002;**123**(1):110-118. doi:10.1067/mtc.2002.119064
17. O'Brien SM, Jacobs JP, Clarke DR, et al. Accuracy of the Aristotle Basic Complexity score for classifying the mortality and morbidity potential of congenital heart surgery operations. *Ann Thorac Surg*. 2007;**84**(6):2027-2037. doi:10.1016/j.athoracsur.2007.06.031
18. Jacobs JP, O'Brien SM, Pasquali SK, et al. The importance of patient-specific preoperative factors: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg*. 2014;**98**(5):1653-1659. doi:10.1016/j.athoracsur.2014.07.029
19. Al-Radi OO, Harrell FE Jr, Caldarone CA, et al. Case

- complexity scores in congenital heart surgery: a comparative study of the Aristotle Basic Complexity score and the Risk Adjustment in Congenital Heart Surgery (RACHS-1) system. *J Thorac Cardiovasc Surg.* 2007;**133**(4):865-875. doi:10.1016/j.jtcvs.2006.05.071
20. Allen P, Zafar F, Mi J, et al. Risk stratification for congenital heart surgery for ICD-10 administrative data (RACHS-2). *J Am Coll Cardiol.* 2022;**79**(5):465-478. doi:10.1016/j.jacc.2021.11.036
 21. O'Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. *J Thorac Cardiovasc Surg.* 2009;**138**(5):1139-1153. doi:10.1016/j.jtcvs.2009.03.071
 22. Jacobs JP, O'Brien SM, Hill KD, et al. Refining The Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model with enhanced risk adjustment for chromosomal abnormalities, syndromes, and noncardiac congenital anatomic abnormalities. *Ann Thorac Surg.* 2019;**108**(2):558-566. doi:10.1016/j.athoracsur.2019.01.069
 23. Ssentongo P, Hehnly C, Birungi P, et al. Congenital cytomegalovirus infection burden and epidemiologic risk factors in countries with universal screening: a systematic review and meta-analysis. *JAMA Netw Open.* 2021;**4**(8):e2120736. doi:10.1001/jamanetworkopen.2021.20736
 24. Shakhgildyan VI. [Congenital cytomegalovirus infection: current issues, possible answers.] *Neonatologiya: Novosti, Mneniya, Obuchenie.* 2020;**8**(4):61-72. doi:10.33029/2308-2402-2020-8-4-61-72 (In Russ.)
 25. Li X, Wang X, Li S, Zeng M, Li D. Viral respiratory infection, a risk in pediatric cardiac surgery: a propensity-matched analysis. *Pediatr Crit Care Med.* 2020;**21**(7):e431-e440. doi:10.1097/PCC.0000000000002308
 26. Barker GM, O'Brien SM, Welke KF, et al. Major infection after pediatric cardiac surgery: a risk estimation model. *Ann Thorac Surg.* 2010;**89**(3):843-850. doi:10.1016/j.athoracsur.2009.11.048
 27. García H, Cervantes-Luna B, González-Cabello H, Miranda-Novales G. Risk factors for nosocomial infections after cardiac surgery in newborns with congenital heart disease. *Pediatr Neonatol.* 2018;**59**(4):404-409. doi:10.1016/j.pedneo.2017.11.014
 28. Kelleher ST, McMahon CJ, James A. Necrotizing enterocolitis in children with congenital heart disease: a literature review. *Pediatr Cardiol.* 2021;**42**(8):1688-1699. doi:10.1007/s00246-021-02691-1
 29. Kessler U, Hau E-M, Kordasz M, et al. Congenital heart disease increases mortality in neonates with necrotizing enterocolitis. *Front Pediatr.* 2018;**6**:312. doi:10.3389/fped.2018.00312
 30. Karin BT, Jaxalykova KK, Chuvakova TK, Kussainov AZ, Altynbayeva GB, Saliyeva SS, Umesheva KA, Berdiyaroova GS, Ashirbay KS, Aitbayeva EB. Alternative to the kangaroo mother care method in preterm infants. *Bangladesh J Med Sci.* 2026;**25**(3):848-855. doi:10.3329/bjms.v25i3.90555.
 31. Burzyńska J, Jaworski R, Maruszewski B, Kansy A, Dzierżanowska-Fangrat K. Perioperative antibiotic prophylaxis in pediatric cardiac surgery: simple is better. *Antibiotics (Basel).* 2023;**12**(1):66. doi:10.3390/antibiotics12010066