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Prediction of childhood cancer using APGAR score: A systematic review and meta-analysis

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ABSTRACT

Background: The etiology of childhood cancer remains unclear, although current research suggests that the uterine environment has a significant impact. The objective of this review is to investigate the 5-minutes and 1-minute APGAR scores as a predictor risk factor for cancer development among the pediatric population. *Methodology:* We performed a systematic literature search on four major databases, PubMed, Google Scholar, Web of Science, and EBSCO to include relevant and eligible studies in this review. The authors used Review Manager 5.4 to conduct a quantitative data synthesis for the condition of interest analyses. *Results:* Thirteen eligible studies and 19517 patients with childhood cancer were included as the population of this study. The low 1-minute and 5-minutes APGAR score (<7) were regarded as significant factors for risk for development of childhood cancer [OR: 1.23, 95% CI (1.1, 1.35), P= 0.000] and [OR: 1.29, 95% CI (1.02, 1.57), P= 0.000], respectively. *Conclusion:* We conclude that low 1-minute and 5-minutes APGAR scores are momentous risk influences for childhood cancer development. We further conclude that the low 1-minute APGAR score potentiated a grander hazard for developing hepatoblastoma and neuroblastoma among the pediatric population. The 5-minutes APGAR score was also a probable risk factor for hepatoblastoma development among children but a protective factor for childhood embryonal tumors development.

Keywords: Childhood cancer; APGAR score; Systematic review; Meta-Analysis

1. BACKGROUND

In developed countries, malignancies are the second chief cause of mortality in children. The introduction and continuous improvement of multimodal treatment strategies, as well as highly specialized diagnostic technologies, have resulted in a welcome, significant rise in the possibility of cure during the most recent decades. Nonetheless, pediatric cancer and the treatment of it remain a challenge for children, their families, and the oncologists who care for them, and from a public health standpoint (Kaatsch, 2010). Despite years of research, the etiology of pediatric cancer remained unclear. Almost half of all

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childhood malignancies are detected prior the age of 1 year, indicating that some risk factors present in utero or the early postnatal period (Kaatsch, 2010; Parkin et al., 2002). However, few of these risk variables have been established. Birth characteristics may suggest interactions between genetic vulnerability and prenatal environmental causes of cancer, although empirical evidence is inconsistent and inconclusive (Greaves, 1999; Tower & Spector, 2007).

Childhood malignancies are a assorted collection of diseases, but three categories are responsible for the majority of identified cases: leukemia, CNS and brain tumors, and lymphomas (Dung et al., 2020; Bahoush et al., 2021; Abudaowd et al., 2021). The five-year survival rate varies by kind of childhood cancer, but in general, 78% of children who were diagnosed with malignancies will be alive in five years. Most varities of childhood malignancies have seen increases in survival, but children with leukemia have made the most progress. Cancer is still the greatest cause of mortality among children, despite a steady drop in mortality rates since 1975 (Hewitt et al., 2003). Several studies in developed countries have projected that cancer incidence prior the 15 years of age increased in the previous decades of the 20th century and early in the new millennium. This has been demonstrated, for example, by the Surveillance, Epidemiology, and End Results (SEER) Programs in the USA (Tomatis, 1989) and a major European multicentric study organized by the (IARC, 2007). In Europe, rates have increased at a rate of 1-2 percent per year, with the increase affecting most cancer types and including adolescents (age 15-19).

Almost every newborn receives an Apgar score, which assesses the clinical condition of the newborn based on five physical indications (heart rate, respiratory effort, reflex irritability, muscular tone, and color) present shortly after birth. A total score of 9 or 10 implies that the baby is in the "finest conceivable situation" (Apgar, 1952). Although the Apgar score's usefulness has been questioned in recent years (Committee on Fetus and Newborn, American Academy of Pediatrics, 1996), it remains the only widely used and approved instrument for measuring the viability of newborn infants worldwide (Papile, 2001). The Apgar score at five minutes is a predictor of newborn death (Casey et al., 2001) as well as various neurological outcomes (Moster et al., 2001; Stuart et al., 2011).

It is hypothesized that children whose Apgar score was low have a advanced threat on behalf of the development of infantile cancer than children with a full Apgar score (Stuart et al., 2011). This meta-analysis aimed to assess and investigate the 5-minutes and 1-minute APGAR scores as a predictor risk factor for cancer development among the pediatric population.

2. METHODOLOGY

This review was conducted and reported following demonstrated guidelines for systematic reviews, Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020).

Study design

This was a systematic review and meta-analysis.

Study duration

From August to September 2021.

Study condition

This study investigates the published literature of APGAR score as a probable threat for developing childhood cancer.

Search strategy

An electronic methodical literature examination of four major databases, PubMed, Google Scholar, Web of Science, and EBSCO, was implemented to include relevant and eligible literature. Our search process was restricted to the English linguistic and was specified for each database as necessary. The relevant researches were recognized over the following keywords that adjusted into Mesh terms in PubMed; "Childhood cancer," "carcinoma," "tumor," "Children," "pediatric population," "1-minute APGAR score", and "5-minutes APGAR score". The relevant keywords were combined with Boolean operators like "OR" and "AND." Full-text publications, freely accessible articles, human trials, and English were involved in the search outcome.

Selection criteria

Our review included the studies with the following criteria

Mainly case-control studies and study designs that provided the 1-minute and 5-minutes APGAR scores of cases who developed cancer and controls or odds ratios of APGAR scores as a predictor for developing childhood cancer.

Only pediatric population <18 years.

Exclusion criteria comprised the following
Studies with adult patients aging 18 years or more.
Studies not conducted in the English language.
Studies with no free access.

Data extraction

Rayyan (Intelligent Systematic Review) (Ouzzani et al., 2016) was used to detect the duplicate evaluation aspects of the systematic search outcomes. By screening the pooled search results using a set of inclusion/exclusion criteria, the researchers assessed titles and abstracts for convenience. The reviewers evaluated the full text of the papers that saw the enclosure standards. Every variances were resolute through debate and discussion by the authors. A data extraction form was built to comprise the eligible research. The authors extracted information about the study titles, authors, study year, study design, study population, participant number (cases and controls), gender, the cancer type, and odds ratios for the available APGAR scores.

Threat of bias evaluation

The Newcastle-Ottawa scale (NOS) (Wells et al., 2000) was used for qualitative and quantifiable data combination for case-control studies to assess the included research quality. The reviewers examined and challenged any differences in the quality evaluation. The funnel diagram was examined visually to establish publication bias.

Strategy for data synthesis

To provide a qualitative overview of the included research aspects and outcome data, summary tables including the collected details from the eligible studies were presented. After the data processing was evaluated, the magnitude of the recommended pooled analyses was investigated. After the data extraction process was completed, decisions were made on how to maximize the usage of case and control data and the numerical data of the included study articles. Independent viability of the pooled meta-analyses and qualitative synthesis of the selected data was conducted. Studies that met the full-text inclusion requirements but did not provide numerical data on the APGAR scores as a probable threat of childhood cancer development were excluded.

The authors used Review Manager 5.4 (Review Manager, 2020) to conduct a quantitative data synthesis for the condition of interest analyses. The APGAR scores as a prospective hazard for cancer development among the pediatric population were evaluated using random-effects meta-analysis. An I^2 statistic was used to measure heterogeneity as an important section of the pooled meta-analysis. To count publication prejudice, the funnel-plot and funnel-plot symmetrical distribution quantities were employed.

3. RESULTS

Search results

The systematic search yielded 684 articles that were extracted from the searched databases, then 87 duplicates were detected and removed. Title and abstract screening were implemented on 597 study articles, and 517 studies were excluded. Eighty reports were sought for retrieval, and only 4 articles were not retrieved. Finally, 76 study articles underwent full-text assessment; 44 studies were excluded for wrong study outcome, 15 studies were excluded for not available numerical data on APGAR scores as a potential threat of childhood malignancy development, and 4 studies were excluded for the wrong population type. Thirteen unique eligible studies were comprised in this analysis. A summary of the study assortment is illustrated in Figure 1.

Characteristics of the involved studies

A total of 13 studies were encompassed in this study, with 19517 patients diagnosed with childhood cancer. Three of them were steered in the Nordic countries (Denmark, Finland, Norway, and Sweden) (Schüz et al., 2011; de Fine Licht et al., 2012; Schmidt et al., 2010), three in Sweden (Källén et al., 2010; Linet et al., 1996; Forsberg & Källén, 1990), two in the USA (Buck et al., 2001; Burningham et al., 2014), one in Scotland (Bhattacharya et al., 2014), one in the United Kingdom (UK) (Fear et al., 2001), one in Brazil (de Paula Silva et al., 2016), one in Finland (Seppälä et al., 2021), one in Australia (Dixon et al., 2018). Most studies have investigated innumerable categories of juvenile malignancies, but Schüz et al., (2011) investigated only Wilms tumor, de Fine Licht et al., (2012) investigated hepatoblastoma, Fear et al., (2001) investigated the malignant neoplasms of the brain, Linet et al., (1996)

investigated brain tumors, Buck et al., (2001) investigated neuroblastoma, Schmidt et al., (2010) investigated CNS tumors, Burningham et al., (2014) investigated CNS, bone, and soft tissue tumors, and Dixon et al., (2018) reported that leukemia was the most common cancer type among their pediatric population (table 1).

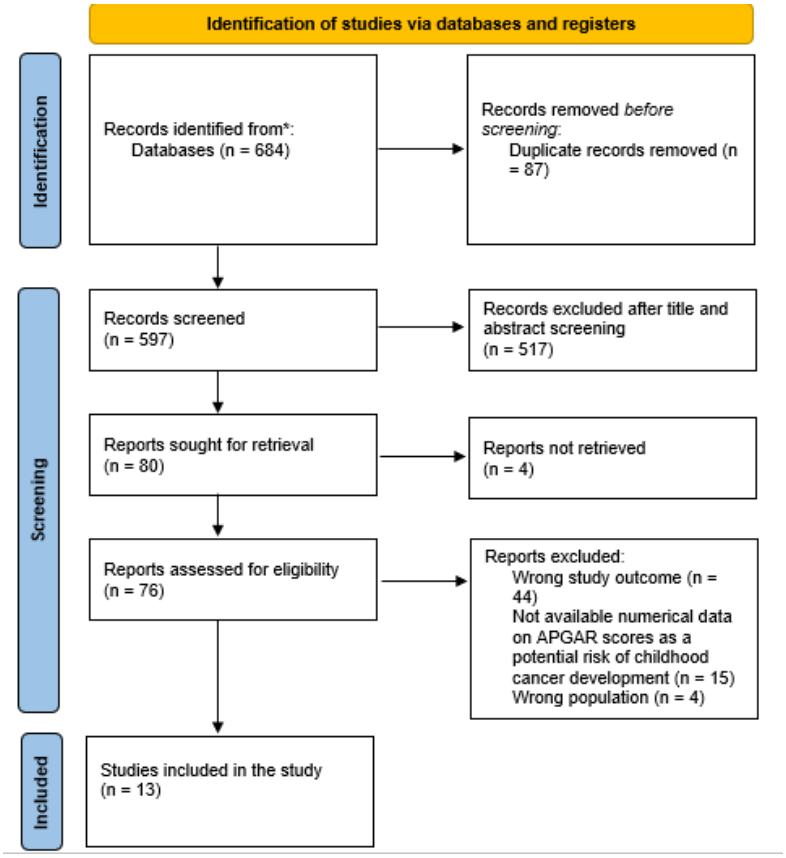


Figure 1 PRISMA flowchart of the study selection process.

Table 1 Summary of characteristics of the included studies.

Study	Study design	Country	Total participants (cases)	Male (%)	Condition	NOS
Bhattacharya et al., 2014	Case-control	Scotland	176	NA	Childhood cancer	7
Schüz et al., 2011	Case-control	Nordic countries	690	326 (47)	Wilms Tumor	8
Källén et al., 2010	Case-control	Sweden	6459	NA	Childhood cancer	7
de Fine Licht et al., 2012	Case-control	Nordic countries	155	96 (61.9)	BuHepatoblastoma	8
Fear et al., 2001	Case-control	UK	83	41 (49.4)	Malignant neoplasms of the brain	6
Linet et al., 1996	Case-control	Sweden	570	280 (49.1)	Childhood brain tumors	7
Buck et al., 2001	Case-	USA	131	NA	Neuroblastoma	6

	control					
de Paula Silva et al., 2016	Case-cohort study	Brazil	340	202 (59.4)	Childhood Embryonal Solid Tumors	9
Schmidt et al., 2010	Case-control	Nordic countries	3,443	1,857 (53.9)	CNS Tumors in Children	8
Seppälä et al., 2021	Case-control	Finland	4058	192 (53.8)	Childhood cancer	8
Burningham et al., 2014	Case-control	USA	1018	565 (55.5)	CNS, bone, and soft tissue tumors in Children	8
Dixon et al., 2018	Case-control	Australia	1126	604 (53.7)	The most common malignancies were leukemia (37.0%), CNS tumors (17.2%), and solid tumors excluding those of renal, hepatic or central nervous system origin (26.8%)	9
Forsberg et al., 1990	Case-control	Sweden	1268		Childhood cancer	7

Analysis of 1-minute APGAR score in predicting childhood cancer development

This analysis showed that a low 1-minute APGAR score (<7) is a momentous hazard influence for the development of childhood cancer [OR: 1.23, 95% CI (1.1, 1.35), P= 0.000]. The 1-minute APGAR score presented a greater risk for developing childhood cancer in de Fine Licht et al., (2012) [OR: 3.1 (0.20, 6.00)] amongst kids identified with hepatoblastoma and [OR: 2.9 (-2.20, 8.00)] amongst kids identified with neuroblastoma in Buck et al., (2001). While, it constituted no effect for predicting bone cancer in Burningham et al., (2014) [OR: 1.00 (0.14, 1.86). No significant inter-heterogeneity between studies was detected (I^2=0%, P=0.89) (figure 2).

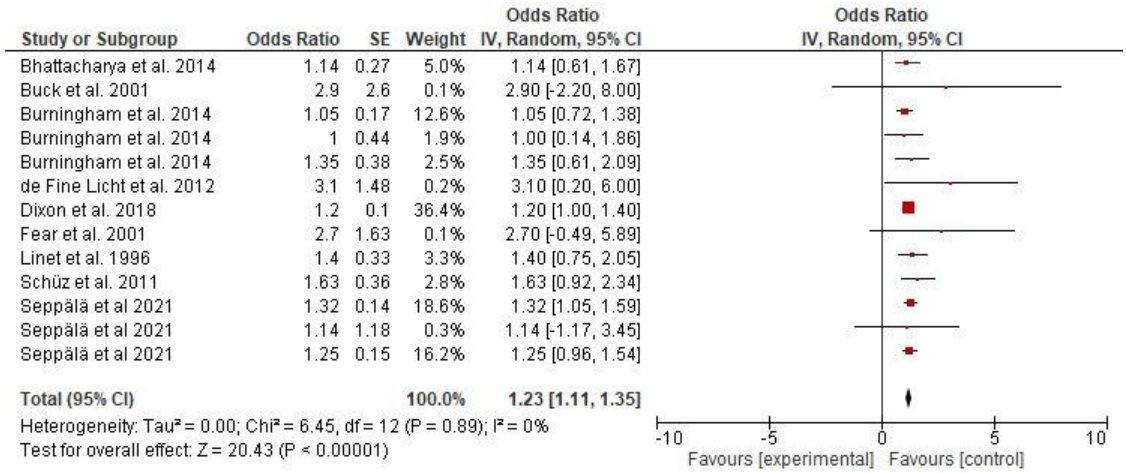


Figure 2 Forest plot of 1-minute APGAR score as a potential predictor for childhood cancer development

Analysis of 5-minutes APGAR score in expecting childhood cancer development

This analysis showed that a low 5-minute APGAR score (<7) is a significant risk factor for developing childhood cancer [OR: 1.29, 95% CI (1.02, 1.57), P= 0.000]. The 5-minute APGAR score presented a greater risk for developing childhood cancer in de Fine Licht et al., (2012) [OR: 7.5 (-7.81, 22.81)] among children diagnosed with hepatoblastoma, while it was a protective factor for childhood embryonal tumors development in de paula silva et al., (2016). No significant inter-heterogeneity between studies was detected (I^2=13%, P=0.31) (figure 3).

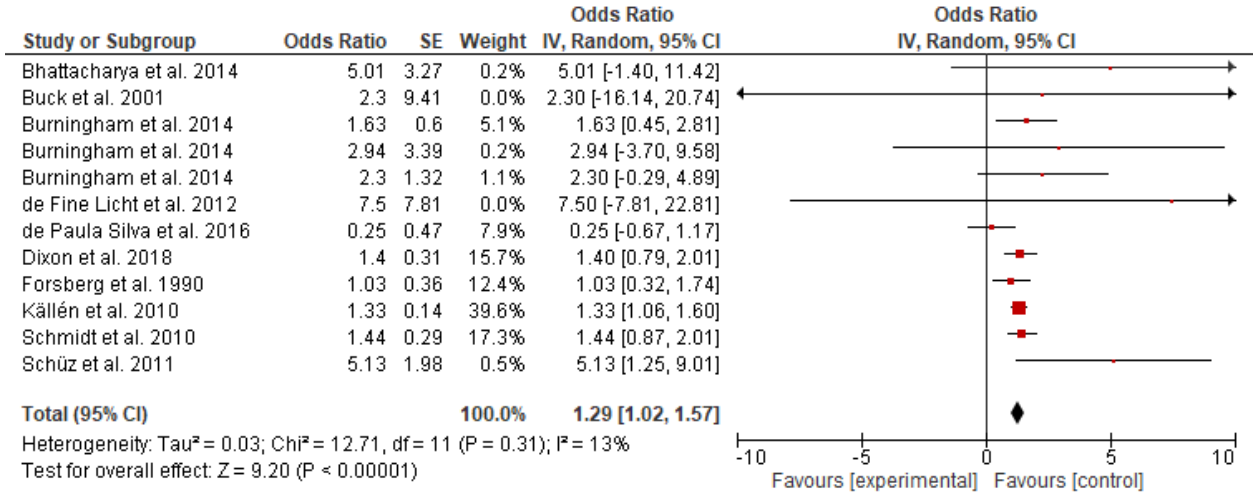
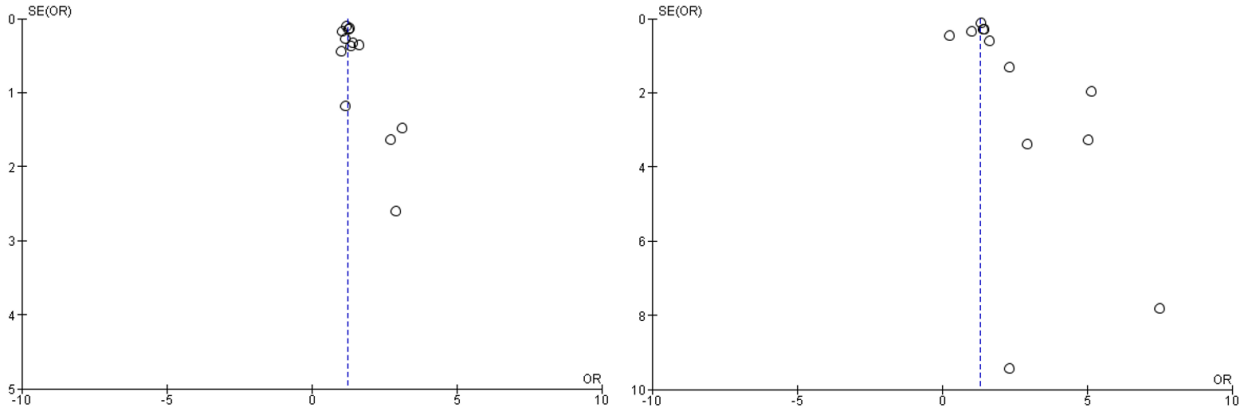


Figure 3 Forest plot of 5-minutes APGAR score as a potential predictor for childhood cancer development

Publication bias detection

Visual inspection of the funnel plots reveals a slightly asymmetrical distribution of the APGAR scores between studies in patients with childhood cancer. Higgin's I^2 test showed no significant heterogeneity among the pooled studies (I^2=0%) Figure (4-a) and (I^2=13%) Figure (4-b).



a) 1 Minute APGAR Score b) 5 Minutes APGAR Score

Figure 4 Funnel plot to assess publication bias of the involved studies.

4. DISCUSSION

Small Apgar score (AS) is marker of characteristics that prevent the child from obtaining a high score or of a suboptimal fetal environment, which may have a programming effect on developing childhood cancer (Gilstrap et al., 1987). It is also possible that neonatal treatments associated with small Apgar score may raise the threat of certain child malignancies (Sadetzki & Mandelzweig, 2009). This meta-analysis investigated the APGAR scores as potential risk factors for childhood cancer development. This study demonstrated that a low 1-minute APGAR score is a significant factor of risk for developing childhood cancer [OR: 1.23, 95% CI (1.1, 1.35)]. Moreover, it potentiated a threat for developing hepatoblastoma (de Fine Licht et al., 2012) and neuroblastoma (Buck et

al., 2001) among the pediatric population, but no effect was noticed among bone cancer patients (Burningham et al., 2014). However, the increased association risks of both retinoblastoma and hepatoblastoma after adjustment may suggest that a low AS has an independent role in these two childhood malignancies.

The biological mechanisms behind the reported relationships between low Apgar score and greater risk of hepatoblastoma are not very clear (Reynolds et al., 2004). The observed association could be attributed to reverse causality, implying that these children were born prematurely, with poor health and LBW (low birth weight) resulting in low Apgar scores due to in utero started carcinogenesis. Because of developmental disruptions during organogenesis, the tumor may begin to form in utero, allowing for an unregulated continuation of proliferation, culminating in immature tissue identified as a hepatoblastoma cancer (Carachi et al., 2008).

The fact that hepatoblastoma incidence rates are inversely related to age, with the highest rates happening in the infacy life, lends credence to this theory. It's even conceivable that the peak in incidence comes during pregnancy. Second, multiple cases of hepatoblastoma tumors have been found in stillborns (Isaacs, 2007) and in live-born infants, some hepatoblastoma tumors form during the first days after delivery, suggesting that some hepatoblastoma tumors originate in utero (Catanzarite et al., 2008). We also demonstrated that a low 5-minute APGAR score is a substantial forecaster and risk factor for the occurance of child malignancies [OR: 1.29, 95% CI (1.02, 1.57)]. A Greater 5-minute APGAR score risk for developing childhood cancer was also found among patients with hepatoblastoma (de Fine Licht et al., 2012) while formed a protective factor among patients with embryonal childhood tumors development (de Paula Silva et al., 2016). A low AS is a sign of a atypical fetal environs besides it might be related to compromised immune responses to tumors (Puumala et al., 2008).

Other unfavorable birth outcomes, which are widely utilized as replacement indicators of the suboptimal prenatal environment to explain the fetal origins of various adult diseases, did not explain the observed relationship between low Apgar scores and childhood malignancy risk (Gluckman & Hanson, 2004). As expected, the findings presented that a low Apgar score was more prevalent among children with bad birth outcomes, which was frequently concomitant by infantile malignancy. However, the increased risks related to lower AS was detected in nearly all subgroups, not just those with poor birth outcomes. Additionally, the relasionship remained reliable across the country, and maternal characteristics studied (Tower & Spector, 2007; Von Behren et al., 2011).

In the current study, the associations between a low AS and several specific children's malignancies are noteworthy. The increased hazards linked to a lower score were seen in practically all baseline characters subgroups, including but not limited to the pregnancies that had adverse birth outcomes. However, the consistent associations across the country and maternal characteristics were not involved in this analysis.

Limitations and strengths

A limitation of the current study is the lack of data on risk factors before or after delivery. However, characteristics associated with a small Apgar score, such as relevant neonatal treatments, maybe in the paths between exposure and outcome and better not be adjusted into the studies. A second drawback is that we were unable to exclude the probability of confounding factors such as postnatal environmental exposures. Third, the count of cases for various childhood malignancies is small, although the total control population were millions.

Our study's most significant strength is its large sample size and comprehensive data on investigated factors. As regards our data, we recommend a more in-depth investigation into the hazard of APGAR scores in different forms of childhood cancer. The cohort approach, which used case-control data to collect high-quality data, reduced the impact of information or bias.

5. CONCLUSION

This review demonstrated that low 1-minute and 5-minutes APGAR scores are substantial risk influences in lieu of childhood malignancies development. We futher conclude that the low 1-minute APGAR score potentiated a greater threat for developing hepatoblastoma and neuroblastoma among the pediatric population. The 5-minutes APGAR score was also a probable risk factor for hepatoblastoma development among children but a protective factor for childhood embryonal tumors development. Apgar score might represent significant implications of the foetal environment on subsequent health in addition to being a well-established evaluation tool in newborn care, meaning that its importance in clinical practice and public health may expand beyond its current application.

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Author Contributions

Authors contributed equally in search implementation as well as data extraction and manuscript writing.

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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