Tumours in the Newborn - A Systematic Review and Review of Grey Literature Exploring Differences in the Types, Treatments, and Outcomes of Neonatal Tumours in High Income versus Low-Middle Income Countries

A thesis submitted in fulfilment for the requirements for the degree of Master of Science by Research in Surgical Sciences.

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Contents

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Abstract

Neonatal Tumours are one of the least researched conditions in paediatrics and pose a significant surgical challenge due to the lack of accessibility to and standardization of treatment, especially in lower income regions of the world. Combining a systematic review and a review of grey literature, this research project explores how the types, treatments, outcomes, and parental perspectives of Neonatal Tumours differ across income levels, and it highlights a lack of literature in Low-Middle Income Countries.

The systematic review aims to examine existing literature regarding Neonatal Tumours. Thirty-four reviews were deemed eligible. These studies collectively reported on 2023 neonatal patients, with 1759 of these patients from High Income Level Countries, 178 of these patients from Upper Middle Income Level Countries, 86 of these patients from Lower Middle Income Level Countries and 0 from Low Income Level Countries. Overall Survival was 79.3%: 79.1% in High Income Level Countries, 71.9% in Upper Middle Income Level Countries, and 98.8% in Lower Middle Income Countries. These differences were found to be statistically significant. However, it is important to note the disparities in available patient data between country income levels. The lack of data in Low-Middle Income Level countries emphasizes a need for more research in these areas of the world.

The review of Case Reports dives into the grey literature on this subject, providing observations on types of tumours, demographics, and outcomes by country income level and discussing the importance of Case Reports in research. Using a novel system of categorization, case reports were sorted into five separate categories based on what each intends to present: Management suggestions/dilemmas (n=31), Diagnostic suggestions/dilemmas (n=16), report of a Unique Presentation of a case (n=12), report of a Rare Case (n=8), and Etiology / Pathogenesis of the disease (n=4).

Chapter 1: Introduction

1.1 What are Neonatal Tumours?

Neonatal Tumours are a diverse group of tumours that are diagnosed within the first 30 days after birth and account for 2% of all childhood cancers (Solanki et al., 2020). Some tumours are congenital, being present at birth, and others manifest at some point within this time period. While many Neonatal Tumours can be histologically benign, even these can be fatal as they often affect vital structures, have potential for airway obstruction, and can significantly complicate delivery. Common Neonatal Tumours include Foetal and Neonatal Germ Cell Tumours, Neuroblastomas, Central Nervous System (CNS) Tumours, Renal Tumours, Retinoblastomas, Hepatoblastomas, and Soft Tissue Sarcomas (Zapata-Tarrés et al., 2014).

1.2 Paediatric Tumour Resection Surgery: The Mainstay of Treatment

Tumour resection surgeries are very important and often lifesaving operations that are critical for survival in many incidences of paediatric cancer, especially in neonates. For cancers that manifest as solid tumours, successful treatment can be dependent on a variety of factors such as the specific type of cancer, how early it is diagnosed, the thoroughness of the surgical removal strategy, or even the aggressiveness of adjuvant treatment (e.g., chemotherapy or radiation). Additionally, in some instances, tumour resection surgery alone may be sufficient to eliminate localized cancers (Gupta et al., 2015). Neonatal Tumours, however, are different from other paediatric cancers in that they pose an interesting surgical dilemma. Neonates are extremely sensitive to chemotherapy and radiation, so the mainstay of treatment for this condition is surgery. Resection of Neonatal Tumours, though almost always necessary, is not straightforward with such a vulnerable patient population. Their size and immature physiology makes standard surgical procedures difficult to conduct, and issues pertaining to thermoregulation, glucose management, airway management, and drug metabolism are just some of the many causes of concern when considering neonatal anaesthesia during surgery (Boyer et. al., 2023). Further complicating matters is the fact that in many instances, especially in lower resource settings where prenatal screening is less frequent, this disease tends to be emergent. When diagnosis is made at birth, care teams may not be prepared to address the host of delivery complications

including respiratory obstructions, haemorrhage, etc. that frequently accompany Neonatal Tumours and require urgent intervention. It is important to consider the fact that since the disease is rare and complex in treatment, resection surgery requires highly specialized training and cannot always be provided to the standard necessary depending on the level of resource setting. Therefore, the next point of discussion is on the many factors that exist as barriers to quality and provision of surgical care for this disease.

1.3 Differences between Income Levels and Barriers to Surgical Care

To examine Neonatal Tumours in the context of global health, we must first understand some important background information. While survival rates for paediatric cancer are relatively high in High Income Countries (HICs), this is not the case in Low-Middle Income Countries (LMICs) due to a variety of factors including, but not limited to, a lack of funding and resources, limited access to hospitals and treatment, and a lack of specialists within the field of paediatric oncology. Previous research to determine the total incidence of childhood cancer worldwide, estimates that around 80% of all diagnosed cases of childhood cancer occur in LMICs (Vu et al., 2022). Out of the 20% of cases of childhood cancer that occur in HICs, the 5-year survival rate of children with cancer is around 80% (Wu et al., 2019). This is drastically different from the 40% 5-year survival rate of children with cancer in LMICs (Wu et al., 2019). Additionally, perioperative mortality rates for paediatric surgery differ vastly between High and Low-Middle Income Countries, to the extent that it is reportedly 100 times higher in LMICs than in HICs (Talabi et al., 2021). Furthermore, a simulation-based study conducted in 2019 estimated that around 43% of paediatric cancers worldwide were undiagnosed and untreated (Ward et al., 2019). A disproportionate burden of such cases was determined to occur in countries within Western Africa and South Asia, for which 57% and 49% of cases were undiagnosed respectively. Comparatively, only 3% of cases in North America and 3% in Western Europe were said to remain undiagnosed (Ward et al., 2019). There are many factors that play a role in creating these discrepancies. For example, one study reports that while a third of the global population resides in Africa and Southern Asia, only 12% of the global surgeons work in these regions (Pulvirenti et al., 2022). Moreover, the ratio of paediatric surgeons to people is strikingly disproportionate, and in 26 African nations it is reportedly about 0.26 to 1,000,000, while the minimum standard ratio is about 1 to 100,000 children. The majority of the paediatric surgeons who do work in

many of these LMICs work in cities, leaving rural areas without access to sufficient paediatric surgical care (Pulvirenti et al., 2022). Finally, it is important to note that a lack of standardization of surgical procedures and limited access to surgical training can also contribute greatly to the low survival and high perioperative mortality rates in paediatric surgery in LMICs, so even if treatments such as chemotherapy are accessible, areas that lack access to specialized and standardized surgical services will have difficulties improving survival rates of children with many types of solid tumours (Geel et al., 2021).

There are several barriers to surgical care that are uniquely exacerbated for Neonatal Tumours. Especially in low resource settings, treatment is not always immediate because of misdiagnosis or delayed referral. One review of malignant solid Neonatal Tumours in Africa reported that 'referral was often delayed pending the exclusion of more commonly seen diseases, consultation with the traditional healer, or by a failure to recognise the nature of the pathology at the referring institution' (Hadley et al., 2002). In one case report from Ethiopia, a child born with a Congenital Thyroid Teratoma wasn't diagnosed until 17 days of age because the parents had to take the child to several different health centres before they were referred to an institution with the capacity to treat this condition at 13 days old (Tigabie et al., 2020). Additionally, where populations rely heavily upon traditional healing or folk medicine with little accessibility to tertiary care centres, patients may not even survive to referral if the tumour type is aggressive (Tigabie et al., 2020). When patients are referred, specialists with the skill and knowledge to treat them may be few and far between; for example, in Malaysia in 2010 there were 'only seven paediatric surgical centres of single-surgeon practice nationwide covering almost half a million live births annually,' (Yeap et al., 2010). Such issues could be avoided through prenatal diagnosis, though accessibility to these services are also lacking in low resource areas. In Burkina Faso, for example, one case reports a newborn with an Orbital Teratoma that was discovered originally through ultrasound, though could not be conclusively diagnosed through prenatal MRI due too insufficient funds (Méda et al., 2020). One final barrier to adequate care is a postoperative factor: loss to follow up (LTFU). According to one review of ten cases of Neonatal Sacrococcygeal Teratoma in India, 'despite meticulous counselling and advice, only 40% of patients came for regular follow-up. In all probability, the children who are LTFU are

well. Hence poor, parents, who are living hand-to-mouth, feel it is an unnecessary effort to bring the child for a medical check-up,' (Sinha et al., 2013).

1.4 Finding the Gaps: What Literature is Lacking?

Interestingly, in both LMICs and HICs, Neonatal Tumours are one area of study within paediatric oncology that remains severely underexplored. While a significant body of research focuses on barriers to general paediatric surgical care in LMICs and the prevalence of common childhood cancers within these regions, there seems to be very little information on differences in incidence, accessibility to treatment, and outcomes of tumours in the newborn.

There is a decent body of research comparing incidence and survival rates of childhood cancer as well as general paediatric surgical care between countries of different income level. However, these studies tend to focus on the epidemiological statistics and treatment of childhood Leukaemia and Hodgkin's Lymphoma which make up some of the most prevalent types of childhood cancer. While these are very important areas of study, both Leukaemia and Lymphoma are cancers of the blood that do not typically manifest as solid tumours and therefore the mainstay of treatment is chemotherapy. In terms of tumour specific observational studies, work has been done investigating Wilms' Tumour in LMICs (Vu et al., 2022). This is a popular area of interest because Wilms' Tumour is the most common malignant abdominal tumour in children, and it accounts for up to 7% of all childhood cancers globally (Gupta et al., 2015). A significant amount of focus has been devoted to studying this because of how common and curable it is (Gupta et al., 2015).

While this research is both informative and impactful for future interventions within surgical practice in LMICs, there seems to be an associated lack of information and study surrounding Neonatal Tumours and corresponding tumour resection surgery in paediatrics as a whole. This gap in the literature has even been identified by previous studies as 'represent[ing] an unknown,' especially in terms of Neonatal Tumour etiology, prognosis, and treatment (Zapata-Tarrés et al., 2014). For literature that does exist, the majority of published articles are Case Reports. Additionally, research pertaining to the types and prevalence of tumours in the newborn and differences between HICs and LMICs when it comes to Neonatal Tumours is scarce, and to the

best of our knowledge there has not yet been a systematic review done to estimate these measures.

1.5 Project Aims, Components, and Hypotheses

To close the gaps within this field of research, my thesis aims to investigate the current types of Neonatal Tumours as well as the provision of Neonatal Tumour resection surgery and to generate epidemiological statistics pertaining to these conditions. In particular, I attempt to determine survival and mortality rates, to evaluate current perioperative practices, and to identify more information about accessibility of treatment as these factors differ between High and Low-Middle Income Countries.

This project was composed of two parts: a systematic review and meta-analysis of retrospective reviews as well as a review of grey literature. Within the systematic review, I aimed to estimate types, treatment, and survival. I additionally determined the Odds Ratios for the association between outcome measures and both country income levels and tumour type. In my review of grey literature, I aimed to gain insights on types of Neonatal Tumours and care practices between different country income levels from Case Reports.

The goal of this project was to ultimately provide more evidence and motivation for the future development and standardization of Neonatal Tumour treatment and for increasing accessibility to these services in LMICs. Original hypotheses for this project were as follows:

1. Germ Cell Tumours, specifically Sacrococcygeal Teratomas, are the most commonly diagnosed Neonatal Tumour.
2. Surgery is the most utilized intervention for the treatment of Neonatal Tumours.
3. Mortality for Neonatal Tumours is higher and survival is lower in LMICs than in HICs.
4. There exist fewer publications pertaining to Neonatal Tumours from LMICs than for HICs.

Chapter 2: A Systematic Review on the Types, Treatment, and Outcomes of Neonatal Tumours in Different Country Income Levels

2.1 Subject of the Review

Review Title: A Systematic Review on the Types, Treatment, and Outcomes of Neonatal Tumours in Different Country Income Levels

Review Question: How do Neonatal Tumour types, treatment, and survival outcomes differ between Low-Middle Income Level Countries compared to High Income Countries.

2.2 Methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The review has been registered in the PROSPERO database (ID: CRD42025636025). As no patient identifiers were disclosed, Institutional Review Board approval was not required for this study.

2.2.1 Search Strategy and Study Screening

A systematic search was performed in three OVID databases: Medline, Embase, and Global Health. The search strategy included four genres of terms: tumours, neonates, surgery, and outcome measures. Terms were adapted for use between each database using database-specific filters (Table 1). This search identified studies reporting outcomes on neonates with tumours. Given the limited quantity of research published on this topic, there was no restriction on publication date for study selection. Deduplication was performed using Endnote, and Screening was then performed in Rayyan. Retrieved studies were screened independently by two reviewers (LB and FL). The titles and/or abstracts of these studies were reviewed to identify studies meeting the inclusion criteria. Discrepancies were resolved through discussion and consultation of a third reviewer (NK). For studies which were accepted through this screening process, full texts were assessed for eligibility by the two screeners, with discrepancies being resolved in the

same manner. Articles that fulfilled all inclusion criteria were used for the final systematic review.

Table 1: Search strategies utilised for each database.

Database name	Search strategy applied
MEDLINE	1 ((tumo?r* or neuroblastoma* or sarcoma* or teratoma* or Wilms* or retinoblastoma* or nephroma* or fibrosarcoma*) adj3 (neonat* or newborn*)).ti,ab,kf. 2 exp Infant, Newborn/ and (hamartoma/ or neoplasms by histologic type/ or neoplasms by site/ or neoplasms, experimental/ or neoplasms, hormone-dependent/ or neoplasms, multiple primary/ or neoplasms, second primary/ or paraneoplastic syndromes/) 3 (surg* or resect* or operati* or procedure* or excis*).ti,ab,kf 4 ablation techniques/ or ambulatory surgical procedures/ or anastomosis, surgical/ or anterior temporal lobectomy/ or assisted circulation/ or bariatric surgery/ or biopsy/ or 'bloodless medical and surgical procedures'/ or body modification, non-therapeutic/ or cardiovascular surgical procedures/ or curettage/ or cytoreduction surgical procedures/ or debridement/ or decompression, surgical/ or deep brain stimulation/ or device removal/ or digestive system surgical procedures/ or dissection/ or drainage/ or elective surgical procedures/ or electrosurgery/ or endocrine surgical procedures/ or extracorporeal circulation/ or fasciotomy/ or hemostasis, surgical/ or keratectomy/ or laparotomy/ or ligation/ or lymph node excision/ or mastectomy/ or metastasectomy/ or microsurgery/ or minimally invasive surgical procedures/ or minor surgical procedures/ or monitoring, intraoperative/ or myotomy/ or neurosurgical procedures/ or ophthalmologic surgical procedures/ or oral surgical procedures/ or orthopedic procedures/ or ostomy/ or otorhinolaryngologic surgical procedures/ or overlapping surgery/ or pelvic exenteration/ or perioperative care/ or perioperative period/ or plastic surgery procedures/ or pneumonectomy/ or prophylactic surgical procedures/ or prosthesis implantation/ or punctures/ or reoperation/ or second-look surgery/ or splenectomy/ or surgery, computer-assisted/ or thoracic surgical procedures/ or transplantation/ or ultrasonic surgical procedures/ or urogenital surgical procedures/ or wound closure techniques/ 5 (morbidit* or prevalence* or incidence* or mortalit* or survival or occurrence*).ti,ab,kf. 6 1 or 2

	7 3 or 4 8 5 and 6 and 7
Embase	1 ((tumo?r* or neuroblastoma* or sarcoma* or teratoma* or Wilms* or retinoblastoma* or nephroma* or fibrosarcoma*) adj3 (neonat* or newborn*)).ti,ab,kf. 2 exp Infant, Newborn/ and (hamartoma/ or neoplasms by histologic type/ or neoplasms by site/ or neoplasms, experimental/ or neoplasms, hormone-dependent/ or neoplasms, multiple primary/ or neoplasms, second primary/ or paraneoplastic syndromes/) 3 (surg* or resect* or operati* or procedure* or excis*).ti,ab,kf 4 ablation techniques/ or ambulatory surgical procedures/ or anastomosis, surgical/ or anterior temporal lobectomy/ or assisted circulation/ or bariatric surgery/ or biopsy/ or 'bloodless medical and surgical procedures'/ or body modification, non-therapeutic/ or cardiovascular surgical procedures/ or curettage/ or cytoreduction surgical procedures/ or debridement/ or decompression, surgical/ or deep brain stimulation/ or device removal/ or digestive system surgical procedures/ or dissection/ or drainage/ or elective surgical procedures/ or electrosurgery/ or endocrine surgical procedures/ or extracorporeal circulation/ or fasciotomy/ or hemostasis, surgical/ or keratectomy/ or laparotomy/ or ligation/ or lymph node excision/ or mastectomy/ or metastasectomy/ or microsurgery/ or minimally invasive surgical procedures/ or minor surgical procedures/ or monitoring, intraoperative/ or myotomy/ or neurosurgical procedures/ or ophthalmologic surgical procedures/ or oral surgical procedures/ or orthopedic procedures/ or ostomy/ or otorhinolaryngologic surgical procedures/ or overlapping surgery/ or pelvic exenteration/ or perioperative care/ or perioperative period/ or plastic surgery procedures/ or pneumonectomy/ or prophylactic surgical procedures/ or prosthesis implantation/ or punctures/ or reoperation/ or second-look surgery/ or splenectomy/ or surgery, computer-assisted/ or thoracic surgical procedures/ or transplantation/ or ultrasonic surgical procedures/ or urogenital surgical procedures/ or wound closure techniques/ 5 (morbidit* or prevalence* or incidence* or mortalit* or survival or occurrence*).ti,ab,kf. 6 1 or 2 7 3 or 4 8 5 and 6 and 7

Global Health	1 ((tumo?r* or neuroblastoma* or sarcoma* or teratoma* or Wilms* or retinoblastoma* or nephroma* or fibrosarcoma*) adj3 (neonat* or newborn*)).ti,ab,mp. 2 exp neonates/ and exp neoplasms/ 3 (surg* or resect* or operati* or procedure* or excis*).ti,ab,mp. 4 surgery/ 5 (morbidit* or prevalence* or incidence* or mortalit* or survival or occurrence*).ti,ab,mp. 6 1 or 2 7 3 or 4 8 5 and 6 and 7

2.2.2 Inclusion and Exclusion Criteria

The patients included in this study were aged 0 to 28 days – per the definition of 'neonate' used by the World Health Organization – with a documented diagnosis of a Neonatal Tumour. It is acknowledged that infants may have been diagnosed but not treated within this period of time, or that the condition may have arisen during this age and not have been diagnosed within the same time period. In such cases, these patients were included in the study. This review aimed to estimate the types, management, and outcomes of Neonatal Tumours across the globe and to compare these between patients of different country income level. Studies that were included contained information about survival or mortality in these patients.

In study selection, there was no restriction on publication dates or language given the already limited quantity of data available on this subject. Studies using consecutive or retrospective sampling were included. Review articles were excluded, as well as opinion pieces, case reports, case series, case-control studies, cross-sectional studies, cohort studies, and randomized control trials that had not recruited their patient population consecutively. Studies that did not report survival or mortality outcomes in Neonatal Tumour patients were excluded as well.

2.2.3 Data Extraction

Studies accepted through the screening process were analysed for data, during which data was extracted using a pre-piloted, standardised Excel sheet. Data was extracted by two reviewers, with discrepancies resolved through discussion and a third reviewer when necessary. The

following data was extracted from these articles: year of publication, title of review, country where patients were treated, period of evaluation, types and quantities of tumours, number of patients in study, sex of patients in study, time period of diagnosis (antenatal or postnatal) of patients, number and type of interventions, deaths due to malignancy, number of preoperative deaths, number of patients intended to receive surgery, deaths due to treatment toxicity, number of patients receiving chemotherapy or radiation, deaths due to surgery, number of patients receiving surgery, number of patients surviving operation, deaths due to metastatic disease, and number of surviving patients.

2.2.4 Risk of Bias (Study Quality) Assessment

The Newcastle-Ottawa Scale was used to assess the risk of bias of each study. Each article was assessed independently by two reviewers. These results were then compared, and discrepancies were resolved through agreement or consultation of a third reviewer. For this assessment, each study was graded on a scale of 9 stars. Studies graded 0-3 stars were considered to have high risk of bias, 4-6 stars moderate risk of bias, and 7-9 stars low risk of bias. Studies were rated on three categories, each with their own criteria: Selection (4 possible stars), Comparability (2 possible stars), and Outcome (3 possible stars).

2.2.5 Data Synthesis and Statistical Analysis

To quantify the extent of statistical heterogeneity, I^2 statistics (0 indicating no heterogeneity, 0-25% low, 25-50% moderate, 50-75% considerable, and 75-100% high heterogeneity) and Cochran's Q test ($p < 0, 10$) were used. Subgroup analyses were used to investigate causes of heterogeneity. A random effects model based on the DerSimonian-Laird method was used to incorporate an estimate of heterogeneity into the calculation of the common effect. To determine the effect of each study on the meta-analysis, a deterministic sensitivity leave-one out analysis was conducted.

Descriptive statistics were determined for the number and types of tumours diagnosed, the number and types of interventions performed, the mortality due to different variables, and the survival of neonates diagnosed with Neonatal Tumours. For categorical variables, such as sex or period of diagnosis, data from all trials was summed and percentages were calculated. For

individual arms, pooled rates and 95% confidence intervals (CI) were calculated. Odds ratios (OR) comparing patients from different county income levels were reported with 95% confidence intervals. *p* values less than 0.05 were considered statistically significant.

To present the results of the meta-analysis, forest plots were constructed. Subgroups were the different country income levels as well as the different tumour categories. World Bank definitions were used to categorize countries as Low Income Countries, Lower Middle Income Countries, Upper Middle Income Countries, and High Income Countries. Whenever Low-Middle Income Countries are referred to (LMICs), this is the grouping of Low, Lower Middle, and Upper Middle Income Countries into one category. Country income level status was determined using the 2024-2025 World Bank Atlas GNI per capita method.

When analysing Mortality and Survival in depth, outcomes were analysed in multiple dimensions: Mortality due to Malignancy, Preoperative Mortality, Treatment Related Mortality, Surgical Mortality, Mortality due to Metastasis, and Postoperative Survival. Subgroup analyses were then done to compare between income levels and tumour types.

To measure the number of patients who succumbed to the disease we created a measure of Mortality due to Malignancy. This encompasses deaths that were not attributable to surgery, alternative treatment, or other external factors. Patients included in this category are those who died pre or postoperatively from symptoms of the disease, complications due to the disease, or from metastasis. To determine Mortality due to Malignancy, data on deaths due to malignancy was extracted from 30 studies (this data was not available for 4 of the studies in this review).

To evaluate the number of deaths that occurred before surgical intervention, we created a measure of preoperative mortality. This is the amount of deaths that occurred before surgery out of the number of patients who were intended to receive surgical intervention. This data was extracted from 29 studies (not available for 5 of the studies in this review).

The measure of Treatment Related Mortality accounts for deaths that occurred due to Systemic Anti-Cancer Therapy (SACT) (chemotherapy or radiotherapy). This includes deaths due to

treatment toxicity, neutropenic sepsis, etc. Patients in this category may or may not have received surgical intervention in addition. This measure was calculated by dividing the number of deaths due to chemotherapy or radiation by the number of patients receiving these treatments. This data was extracted from 28 studies (not available for 6 of the studies in this review).

Surgical Mortality is a measure of deaths occurring due to a surgical intervention. In this measure we included deaths during or directly following surgical interventions such as partial or complete resection of a tumour, repair of surrounding or affected tissues, and even minimally invasive procedures such as biopsies. Patients in this category may or may not have received adjuvant treatment. This measure was calculated by dividing the number of deaths attributable to surgical intervention by the number of patients receiving surgery. This data was extracted from 29 studies (not available for 5 of the studies in this review).

A measure of Mortality due to Metastasis was created to assess the quantity of deaths attributable to the progression of the disease. Included in this category are patients, regardless of treatment type or status, who succumbed to a spread of their tumours / a widespread or metastatic progression of their cancer. To determine Mortality due to Metastasis, data on patients who died of metastatic disease was extracted from 28 studies (this data was not available for 6 of the studies in this review).

The final measure that was analysed was Postoperative Survival, which accounts for all patients who survived surgical intervention. This measure is the direct inverse of Surgical Mortality and was calculated by dividing the number of patients surviving surgery by the number of patients receiving surgery. This data was extracted from 29 studies (not available for 5 of the studies in this review).

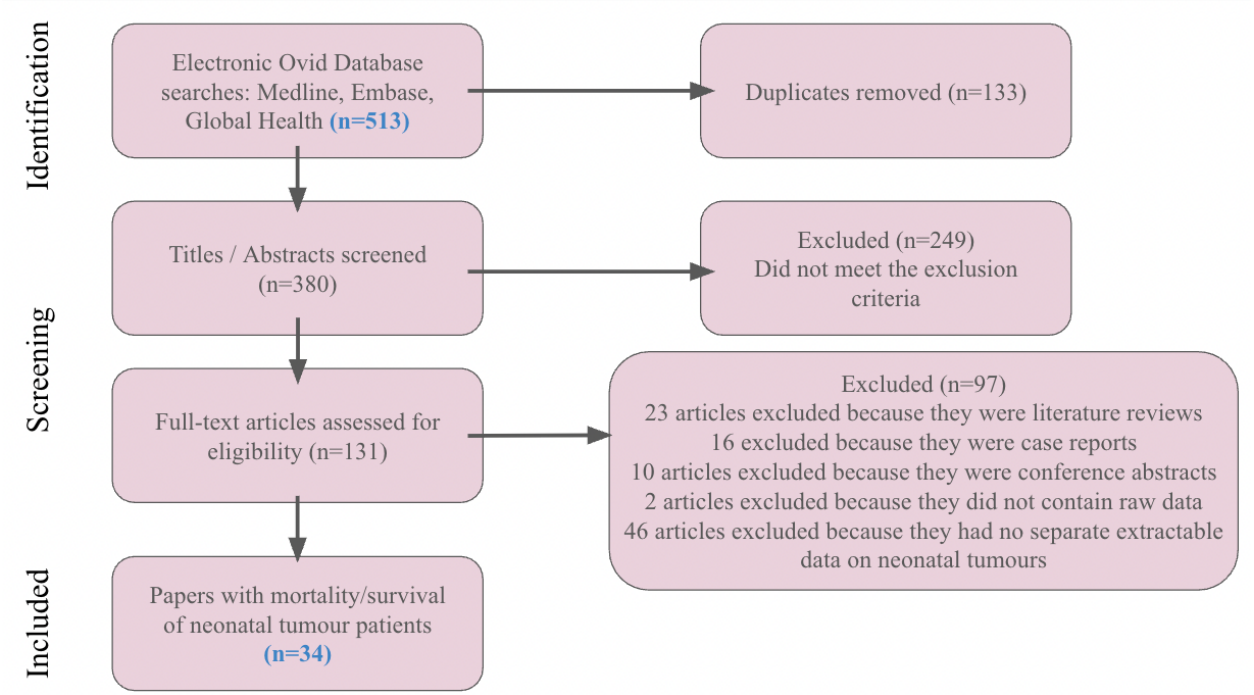
2.3 Results

2.3.1 Study Search and Study Characteristics

The literature search that was conducted resulted in 513 articles. 133 duplicates were found, so 380 articles underwent title and abstract screening, 131 articles underwent full text screening,

and 34 articles were included in the final analysis (Figure 1). All 34 of these articles were retrospective reviews.

Figure 1: Prisma Flowchart



The risk of bias assessment using the Newcastle-Ottawa Scale resulted in 24 fair quality papers of medium risk of bias and 10 high quality papers with low risk of bias.

Figure 2: Risk of Bias in 34 Review Papers

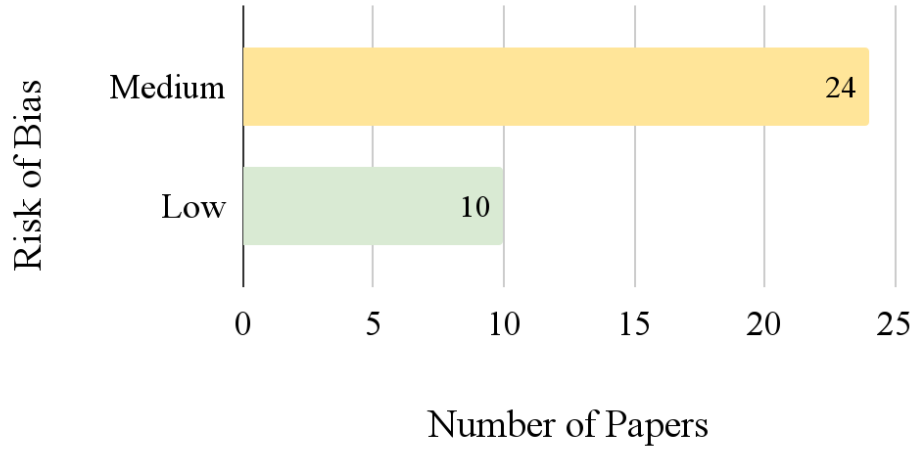
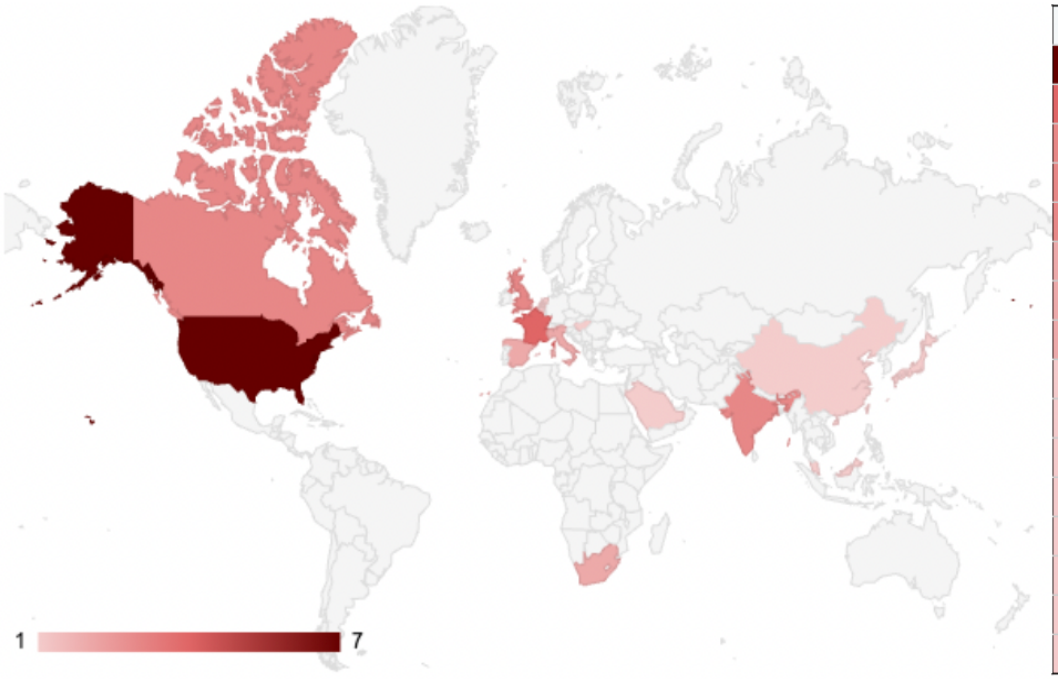


Table 2: Newcastle-Ottawa Ratings for 34 Review Papers

Study		Selection				Comparability		Outcome			Total score	
ID	Income Level	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis 1	Comparability of Cohorts on the Basis of Design or Analysis 2	Assessment of Outcome	Follow-Up Long Enough for Outcomes to Occur?	Adequacy of Follow-Up of Cohorts	*/9	Risk of Bias
1	High	*	0	*	*	0	0	*	*	*	6/9	Medium
2	High	*	0	*	*	*	0	*	*	*	7/9	Low
3	High	*	0	*	*	0	0	*	*	*	6/9	Medium
4	High	*	0	*	*	0	0	*	*	*	6/9	Medium
5	High	*	0	*	*	0	0	*	*	*	6/9	Medium
6	High	*	0	*	*	0	0	*	*	*	6/9	Medium
7	High	*	0	*	*	0	0	*	*	*	6/9	Medium
8	High	*	0	*	*	0	0	*	*	*	6/9	Medium
9	High	*	0	*	*	0	0	*	*	*	6/9	Medium
10	Upper Middle	*	0	*	*	0	0	*	*	*	6/9	Medium
11	High	*	0	*	*	0	0	*	*	*	6/9	Medium
12	High	*	0	*	*	0	0	*	*	*	6/9	Medium
13	High	*	0	*	*	0	0	*	*	*	6/9	Medium
14	High	*	0	*	*	0	0	*	*	*	6/9	Medium
15	Upper Middle	*	0	*	*	0	0	*	*	*	6/9	Medium
16	High	*	0	*	*	0	0	*	*	*	6/9	Medium
17	High	*	0	*	*	0	0	*	*	*	6/9	Medium
18	High	*	0	*	*	*	0	*	*	*	7/9	Low
19	High	*	0	*	*	*	0	*	*	*	7/9	Low
20	High	*	0	*	*	*	0	*	*	*	7/9	Low
21	High	*	0	*	*	0	0	*	*	*	6/9	Medium
22	High	*	0	*	*	*	0	*	*	*	7/9	Low
23	High	*	0	*	*	0	0	*	*	*	6/9	Medium
24	High	*	0	*	*	*	0	*	*	*	7/9	Low
25	Upper Middle	*	0	*	*	0	0	*	*	*	6/9	Medium
26	Lower Middle	*	0	*	*	0	0	*	*	0	5/9	Medium
27	Upper Middle	*	0	*	*	*	0	*	*	*	7/9	Low
28	High	*	0	*	*	*	0	*	*	*	7/9	Low
29	High	*	0	*	*	*	*	*	*	*	8/9	Low
30	High	*	0	*	*	0	0	*	*	0	5/9	Medium
31	Lower Middle	*	0	*	*	0	0	*	*	0	5/9	Medium
32	High	*	0	*	*	0	0	*	*	*	6/9	Medium
33	Lower Middle	*	0	*	*	0	0	*	*	*	6/9	Medium
34	High	*	0	*	*	*	0	*	*	*	7/9	Low

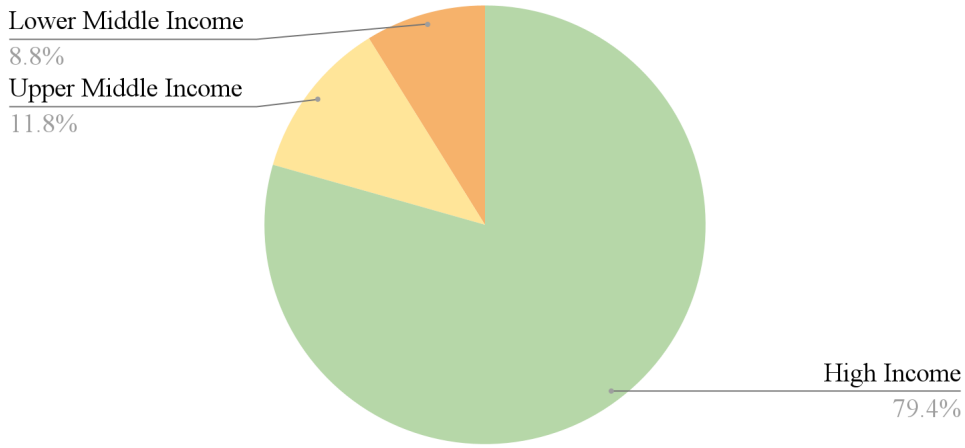
16 Countries were identified (Figure 3). Reviews were sorted by the country in which patients received treatment, and these were stratified by income using World Bank classifications. 79.4% (n=27) of reviews were from High Income Countries, 11.8% (n=4) were from Upper Middle Income Countries, 8.8% (n=3) were from Lower Middle Income Countries, and 0% (n=0) were from true Low Income Countries (Figure 4).

Figure 3: Heatmap of the Number of Studies by Country



# of Studies	Country
7	USA
4	France
3	Canada
3	United Kingdom
3	India
2	South Africa
2	Spain
2	Italy
1	Japan
1	Saudi Arabia
1	Hungary
1	Belgium
1	Malaysia
1	China
1	Netherlands
1	Taiwan

Figure 4: Percentage of Reviews by Country Income Level



2.3.2 Assessment of Heterogeneity

To determine the extent of statistical heterogeneity, we looked at I^2 statistics, Cochran's Q test, and Tau^2. Initially, these calculations were not feasible due to zero variance (100% survival rate) in two studies causing infinite weights. To avoid excluding studies from this assessment, a continuity correction was applied, adjusting the proportions slightly to avoid zero variance. With

a Q value of 311.1, there is substantial observed variability in our reviews. A p value < 0.001 suggests that heterogeneity is statistically significant. The I^2 value of 89.4% supports this conclusion, as any I^2 statistic between 75 and 100% indicates high heterogeneity, and a Tau^2 value of 0.01 indicates moderate variance between studies. The following forest plot (Figure 5) shows survival rates and 95% confidence intervals for each individual study. The red dashed line represents the random effects pooled survival rate across studies. Survival rate effect sizes for each study are annotated.

Figure 5: Forest Plot of Pooled Survival and Survival by Study (with 95% CI)

A DerSimoian-Laird Random Effects model was run to incorporate an estimate of heterogeneity into the calculation of the common effect. This pooled survival rate is consistent with our prior estimates, and heterogeneity remains high. Subgroup-specific pooled survival rates were also calculated.

Table 3: *DerSimonian-Laird Random Effects Model Results*

Income Level	**Pooled Survival Rate (%)**	**95% CI**	**Tau²**	**Q**	**p-value**	**I² (%)**
Overall	78.6	73.9-83.3	0.01	311.07	0	89.4
High Income	76.7	71.5-81.9	0.01	198.04	< 0.001	86.9
Upper Middle Income	75.1	58.3-91.9	0.03	26.10	< 0.001	88.5
Lower Middle Income	98.3	95.6-101	0	0.54	0.76	0

A leave one out sensitivity analysis was also conducted to determine the effect of each study on the meta-analysis. The results conclude that no single study impacts the overall survival rate disproportionately, as the pooled survival rate remains stable between 77.85% to 80.22%. Confidence Intervals and Tau² values remain consistent across exclusions.

Table 4: Deterministic Sensitivity Analysis Results

Left Out Study ID	**Pooled Survival Rate (%)**	**95% CI Lower**	**95% CI Upper**	**Tau²**
1	78.76	74.03	83.49	0.01436
2	79.42	74.78	84.06	0.01369
3	80.22	75.88	84.55	0.01117
4	78.43	73.66	83.19	0.01446
5	79.49	74.83	84.14	0.01361
6	78.51	73.74	83.27	0.01446
7	78.54	73.72	83.36	0.01464

8	78.42	73.63	83.21	0.01452
9	79.1	74.48	83.9	0.01396
10	79.07	74.35	83.8	0.01396
11	78.63	73.84	83.41	0.01447
12	78.14	73.31	82.97	0.01471
13	77.98	73.05	82.92	0.01545
14	78.81	74.07	83.54	0.01434
15	79.49	74.85	84.14	0.01345
16	78.66	73.86	83.47	0.01451
17	79.12	7.44	83.84	0.01406
18	78.05	73.18	82.91	0.0149
19	78.89	74.17	83.6	0.01429
20	78.59	73.78	83.4	0.01458
21	78.86	74.09	83.63	0.01425
22	78.7	73.92	83.47	0.01442
23	79.41	74.86	83.95	0.01256
24	78.14	7.32	83.07	0.01545
25	78.08	73.26	82.91	0.01468
26	78.07	73.28	82.87	0.01451
27	78.34	73.52	83.17	0.01467
28	77.85	72.77	82.92	0.01653
29	78.26	73.27	83.26	0.0159
30	78.55	73.76	83.33	0.0145

31	77.87	73.03	82.71	0.01473
32	78.89	74.17	83.6	0.01429
33	77.88	7.32	82.57	0.01354
34	77.97	73.07	82.86	0.01514

Finally, a Freeman-Tukey double arcsine transformation was used to stabilize variance and ensure that zero variance events did not skew results. The resulting pooled survival estimate is consistent with previous analyses at 78.4% (95% CI: 72.8%–83.5%). The Tau^2 value of 0.11 indicates moderate variability between studies.

2.3.3 Patient Characteristics

Data was collected for 2023 patients with Neonatal Tumours total. There were 536 males, 652 females, and 835 patients for whose sex was unspecified, leaving a male to female ratio of 1 to 1.22.

The proportion of patients from High Income Countries was 87% (n=1759), from Upper-Middle Income Countries was 8.8% (n=178), from Lower-Middle Income Countries was 4.2% (n=86), and from Low Income Countries was 0% (n=0).

18 types of tumours were identified in these studies, which were grouped into larger categories: Germ Cell Tumours (GCT) (n=796), Central Nervous System (CNS) Tumours (n=79), Soft Tissue Tumours (n=364), Renal Tumours (n=44), Neuroblastomas (n=584), Retinoblastomas (n=31), Hepatoblastomas (n=45), and Other (n=80) (Figure 5).

Figure 6: Breakdown of Patients by Tumour Category

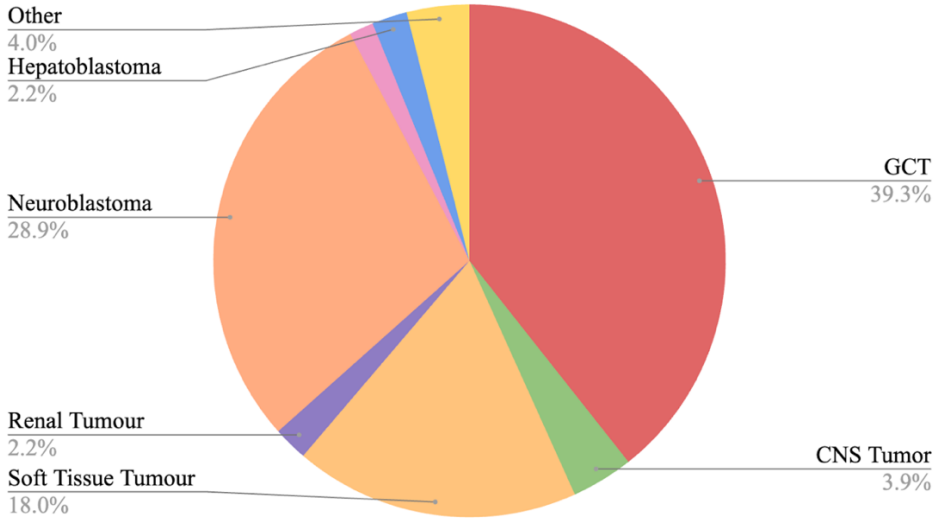


Table 5: Number and Percentage of Patients by Tumour Category and Subcategory

Tumour Category	Tumour Subcategory	# of Patients	% of Tumour Category
GCT	Sacrococcygeal Teratoma	532	66.83
	Cervical Teratoma	45	5.65
	Retroperitoneal Teratoma	7	0.88
	Stomach Teratoma	1	0.13
	Yolk Sac Tumour (YST)	1	0.13
	Miscellaneous	210	26.39
CNS Tumour	Miscellaneous	79	100
Soft Tissue Tumour	Fibrosarcoma	23	6.32
	Rhabdomyosarcoma	19	5.22
	Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)	15	4.12
	Miscellaneous	307	84.34
Renal Tumour	Wilms' Tumour	6	13.64
	Mesoblastic Nephroma	5	11.36

	Miscellaneous	33	75
Neuroblastoma	Neuroblastoma	584	100
Retinoblastoma	Retinoblastoma	31	100
Hepatoblastoma	Hepatoblastoma	45	100
Other	Miscellaneous	80	100

Table 6: Number of Patients by Tumour Category and Country Income Level

Tumour Category	High Income	Upper Middle Income	Lower Middle Income	Total
GCT	659	64	73	796
CNS Tumour	79	0	0	79
Soft Tissue Tumour	327	29	8	364
Renal Tumour	32	11	1	44
Neuroblastoma	520	64	0	584
Retinoblastoma	31	0	0	31
Hepatoblastoma	36	9	0	45
Other	75	1	4	80
Total	1759	178	86	2023

Data for the proportions of patients diagnosed antenatally vs. postnatally was also collected. 20.4% of patients were diagnosed antenatally (n=413), 59.5% of patients were diagnosed postnatally (n=1203), and for 20.1% the time period of diagnosis was not reported (n=407). The ratio of antenatal to postnatal diagnosis is 1:2.91.

Table 7: Time Period of Diagnosis by Country Income Level

Country Income Level	Antenatal (n)	Antenatal (%)	Postnatal (n)	Postnatal (%)
High income	387	27.8	1007	72.2
Upper middle income	10	7.3	126	92.7
Lower Middle Income	16	18.6	70	81.4

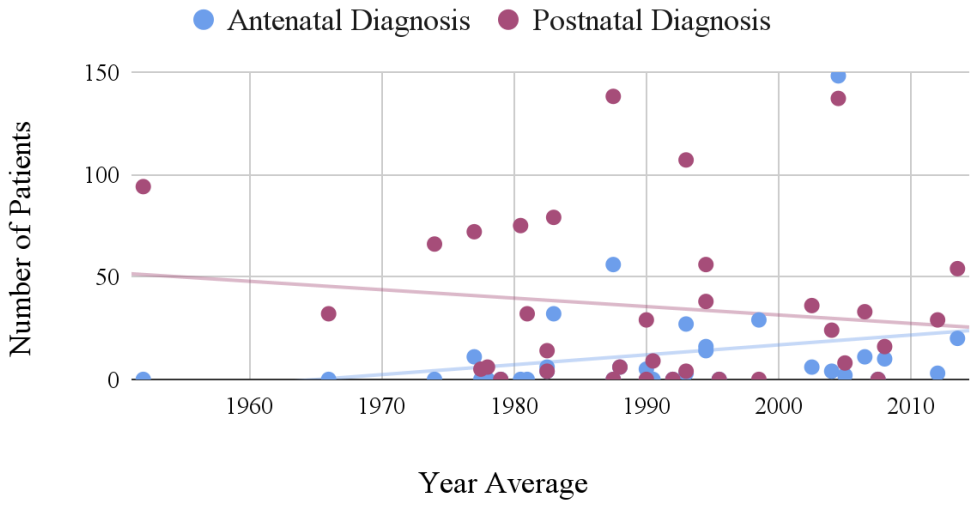
A Chi-square test resulting in a p value of 4.06×10^{-7}shows that there is a highly statistically significant difference in the distribution of antenatal and postnatal diagnosis by country income level. Pairwise T-tests comparing differences between the distributions of antenatal and postnatal diagnosis by country income levels were found to be highly statistically significant for High vs. Upper Middle Income Countries even after a Bonferroni Adjustment ($p<0.001$).

Table 8: Pairwise T-test: Antenatal / Postnatal Diagnosis Proportions by Country Income Level

Comparison	p-value	Bonferroni Adjusted p-value
High Income vs Upper Middle Income	3.77E-07	1.13E-06
High Income vs Lower Middle Income	0.08	0.25
Lower Middle Income vs Upper Middle Income	0.02	0.06

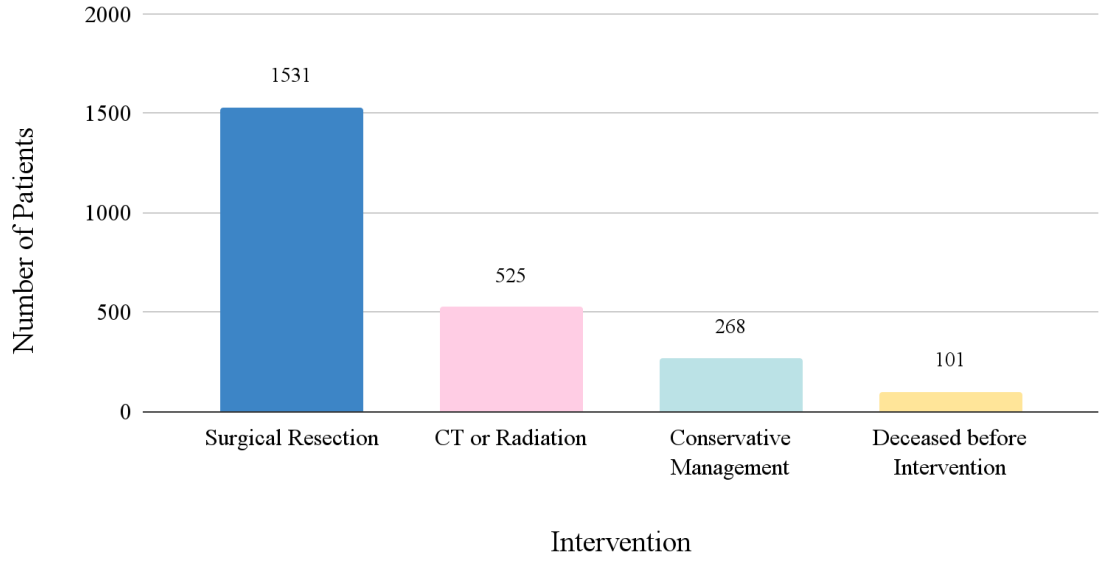
Figure 7 shows antenatal vs. postnatal diagnosis over time. The year for each data point is taken from the averages of the period of evaluation for which data was collected for each study.

Figure 7: Antenatal vs Postnatal Diagnosis Over Time



In terms of interventions, 75.7% of patients (n=1531) received surgical intervention, 26% (n=525) received Chemotherapy (CT) or Radiation, 13.3% of patients (n=268) were reported to have been managed conservatively, and 5% (n=101) died prior to possible intervention. There is overlap in these percentages, as some patients received more than one type of treatment. Only 24 studies contained separable statistics for these interventions, so here we report them as totals instead. Additionally, only 27 studies reported measures of conservative management, and only 30 reported preoperative deaths.

Figure 8: Breakdown of Patients by Intervention



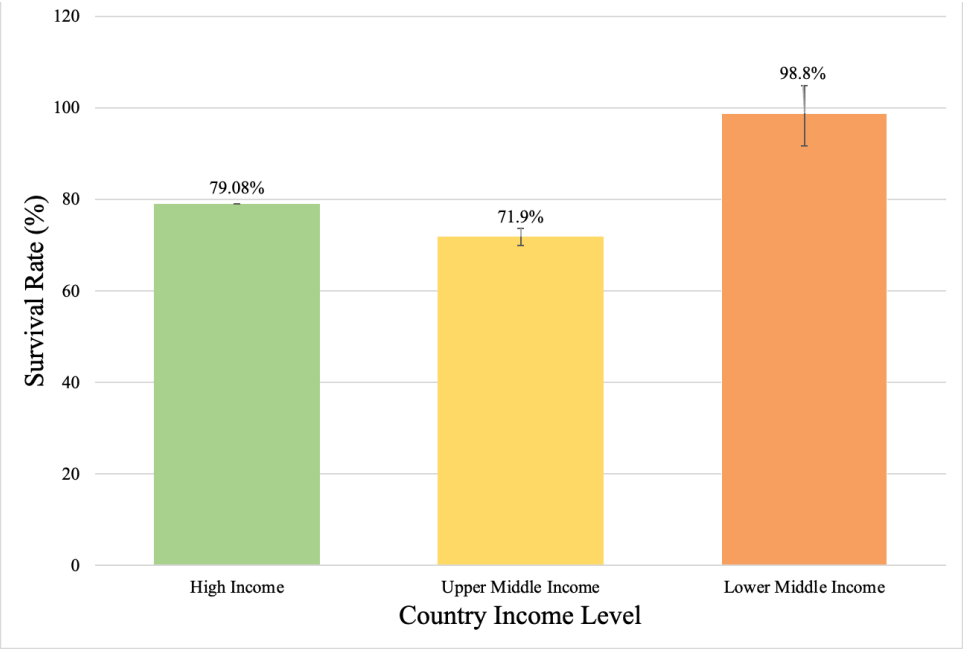
2.3.4 Primary Outcomes

All 34 studies provided data on overall patient survival. The overall patient survival was 79.3% (95% CI = 77.5% to 81.1%) (n=1604). Follow-up duration was not recorded due to variability in data reporting. Comparing between different income level brackets found that High Income Countries had a survival rate of 79.1% (n=1391), Upper Middle Income countries had a survival rate of 71.9% (n=128), and Lower Middle Income Countries had a survival rate of 98.8% (n=85).

Table 9: Overall Survival Rates by Country Income Level

Country Income Level	Survived (n)	Total Patients (n)	Survival Rate (%)	95% CI
High Income	1,391	1,759	79.1	77.1 - 80.9
Upper Middle Income	128	178	71.9	64.9 - 78.0
Lower Middle Income	85	86	98.8	93.7 - 99.8
Total	1604	2023	79.3	75.5-81.1

Figure 9: Overall Survival Rates by Country Income Level (with 95% CI)

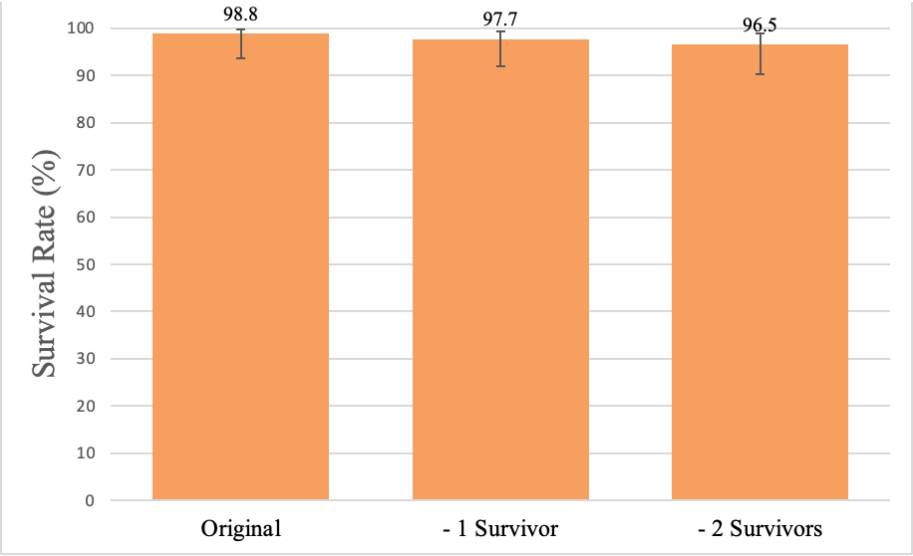


A Chi-square test ($p < 0.001$) showed the differences between survival rates across country income levels to be statistically significant. Post-hoc pairwise comparisons confirmed the difference between the overall survival rate in High Income Countries and Upper Middle Income Countries was statistically significant ($p = 0.02$). **The survival rate in Lower Middle Income Countries is significantly higher than in both Upper Middle and High Income Countries ($p<0.001$). However, the significantly smaller sample size for Lower Middle Income Countries makes this result questionable.** To assess this effect, an Effect Size Sensitivity Analysis was conducted by simulating one or two more deaths in the Lower Middle Income Countries category to determine how survival might be affected. The results in Table 9 and Figure 10, demonstrate that even one or two additional deaths reduce survival and widen the confidence interval, suggesting fragility due to such a small sample size.

Table 10: Effect Size Sensitivity Analysis for Overall Survival in Lower Middle Income Countries

Scenario	Survival Rate (%)	95% CI
Original	98.8	93.7 - 99.8
-1 Survivor	97.7	91.9 - 99.4
-2 Survivors	96.5	90.2 - 98.8

Figure 10: Sensitivity Analysis for Survival in Lower Middle Income Countries (with 95% CI)



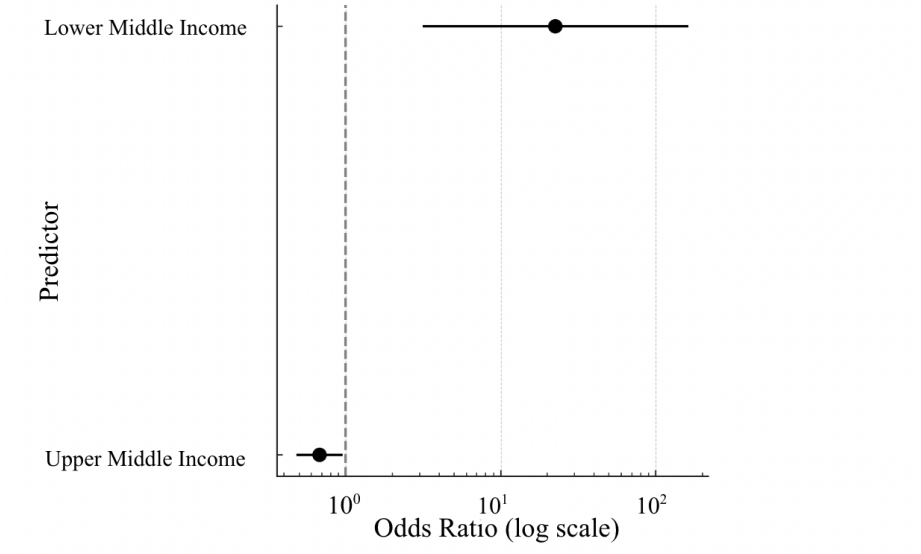
A logistic regression (Table 11) was run to assess how country income level might predict Neonatal Tumour patient survival. With High Income Countries as the intercept, Upper Middle Income Countries showed significantly lower odds of survival than High Income Countries, with a coefficient of –0.39 and an Odds Ratio of 0.68 (p=0.027). Lower Middle Income Countries showed significantly higher odds of survival than High Income Countries, with a coefficient of +3.11 and an Odds Ratio of 22.49 (p=0.002). Due to the small sample size these results should be viewed with caution.

Table 11: Logistic Regression Results for Survival by Country Income Level

Comparison	Coefficient (95% CI)	Odds Ratio (95% CI)	p-value
Intercept (High Income)	1.33 (1.22–1.45)	3.78 (3.37–4.24)	<0.001
Upper Middle vs High Income	–0.39 (–0.74–0.04)	0.68 (0.48–0.96)	0.027
Lower Middle vs High Income	+3.11 (1.14–5.09)	22.49 (3.12–162.03)	0.002

Figure 11 is a forest plot depicting the odds ratios for survival by country income level with confidence intervals. As the High Income Countries group is the reference group, it is indicated at the baseline (odds ratio = 1 on the log scale).

Figure 11: Odds Ratios for Survival by Country Income Level

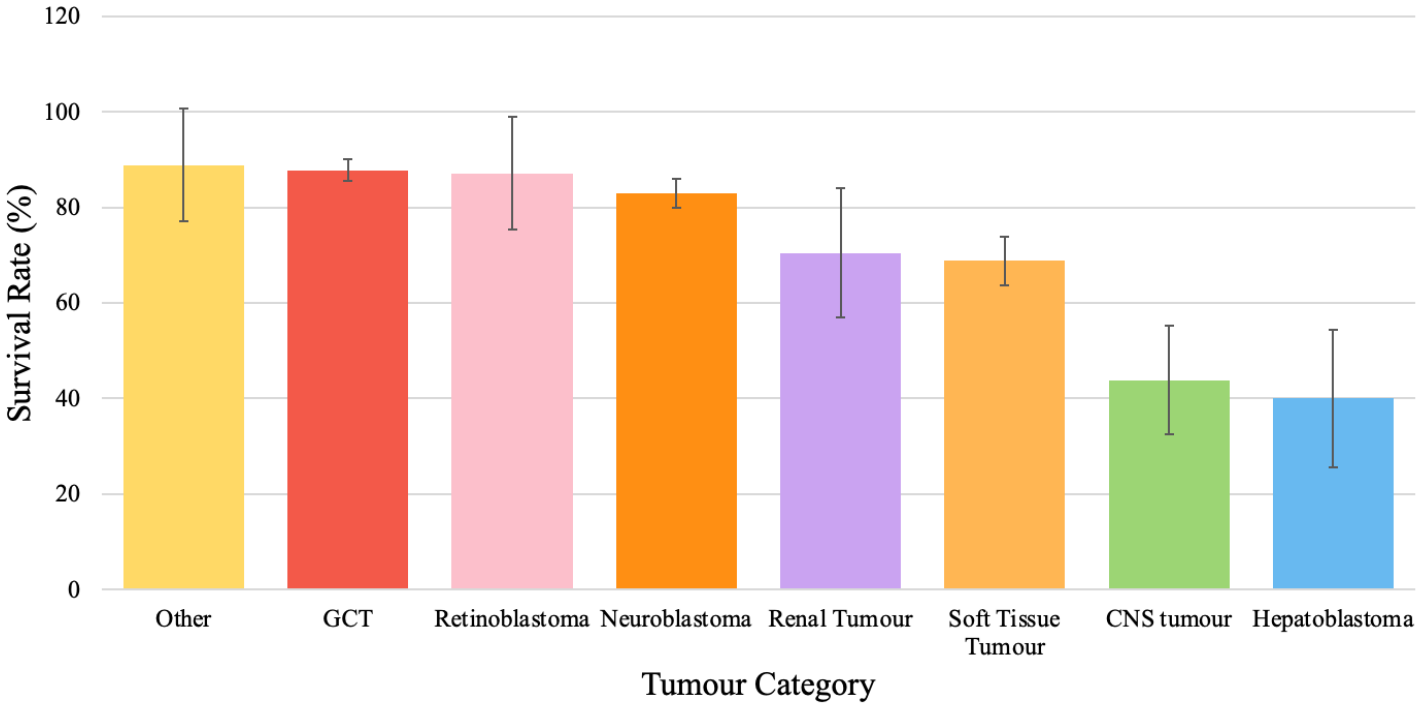


For the next subgroup analysis, a survival comparison was done between tumour categories.

Table 12: Overall Survival by Tumour Category

Tumour Category	Survived	Total Patients	Survival Rate	95% CI
GCT	688	784	87.8%	85.5 - 90.1
CNS Tumour	32	73	43.8%	32.5 - 55.2
Soft Tissue Tumour	223	324	68.8%	63.8 - 73.9
Renal Tumour	31	44	70.5%	57.0 - 83.9
Neuroblastoma	471	568	82.9%	79.8 - 86.0
Retinoblastoma	27	31	87.1%	75.3 - 98.9
Hepatoblastoma	18	45	40.0%	25.7 - 54.3
Other	24	27	88.9%	77.0 - 100.7

Figure 12: Overall Survival Rate by Tumour Category (with 95% CI)



A Chi-square test showed the association between tumour category and survival outcome to be statistically significant ($p < 0.001$). Pairwise T-tests were run comparing each combination of tumour categories (see appendix). CNS tumours had statistically worse survival ($p<0.05$) than all tumour categories except for Hepatoblastoma and Renal Tumours. Additionally, GCTs and Neuroblastomas had statistically better survival than most other tumour categories: specifically CNS tumours, Hepatoblastomas, Renal Tumours, and Soft Tissue Tumours.

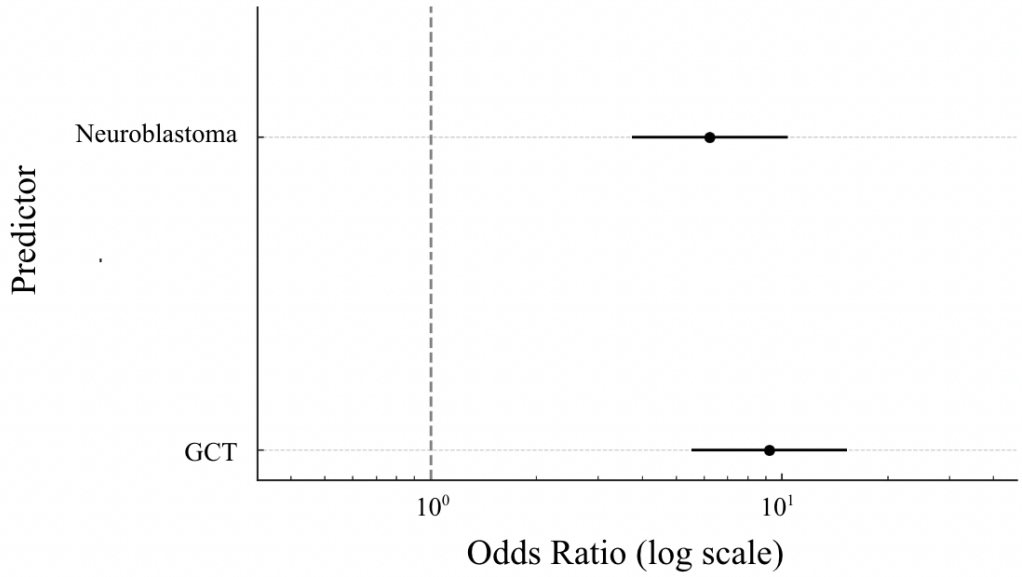
Next, a standard logistic regression was run to analyse survival by tumour category. CNS Tumour was the reference group, as its low survival rate made for clear contrasts. The only tumour category that did not show a statistically significant difference in survival from CNS Tumours was Hepatoblastomas ($p=0.68$). GCT and Neuroblastoma patients showed significantly higher odds of survival ($p<0.001$) than CNS Tumour patients. The category with the highest survival odds ($p<0.001$) compared to CNS Tumours was Other, and patients under this category had 10.25 times higher odds of survival.

Table 13: Logistic Regression Results for Survival by Tumour Category

Tumour Category	**Coefficient**	**Odds Ratio (95% CI)**	**p-value**
Intercept (CNS Tumour)	-0.25	0.78 (0.49-1.24)	0.29
GCT	2.22	9.18 (5.52-15.28)	<0.001
Neuroblastoma	1.83	6.22 (0.40-1.82)	<0.001
Other	2.33	10.25 (3.73-10.37)	<0.001
Hepatoblastoma	–0.16	0.85 (2.83-37.09)	0.68

Figure 13 shows a forest plot that depicts the odds ratios for survival by tumour category with confidence intervals. As the CNS Tumour group is the reference group, it is indicated at the baseline (odds ratio = 1.0 on the log scale).

Figure 13: Odds Ratios for Survival by Tumour Category



2.3.5 Mortality and Survival in Depth

Mortality Due to Malignancy

Across all studies, the Mortality Due to Malignancy was determined to be 12.86%. Table 12 shows this measure by Country Income Level.

Table 14: Mortality Due to Malignancy by Country Income Level

Country Income Level	Deaths Due to Malignancy	Total Patients	Mortality Due to Malignancy (%)	95% CI
High Income	154	1,137	13.5	11.7 - 15.7
Upper Middle Income	26	178	14.6	10.2 – 20.5
Lower Middle Income	0	86	0.00	0.0 - 4.3
Total	180	1401	12.9	11.1 - 14.6

Statistical comparisons were run to evaluate the differences between income levels for this measure. For High vs Upper Middle Income Countries, a Chi square test ($p = 0.79$) revealed no significant difference. For High vs Lower Middle Income Countries and Upper vs Lower Middle

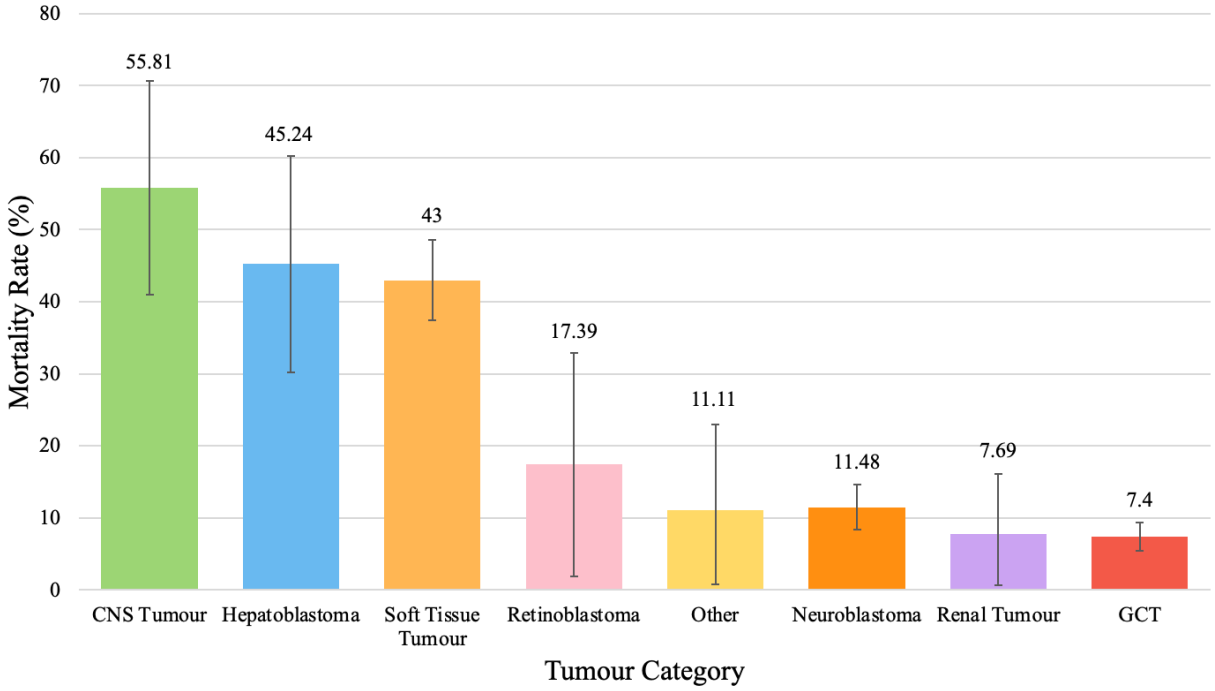
Income Countries, Fisher's exact test was used to try and mitigate the small sample size. For both comparisons, $p < 0.001$ was found, suggesting a significant difference in the mortality between these groups. However, the 0% mortality rate for Low Middle Income countries remains statistically unconvincing due to the small sample size.

Mortality Due to Malignancy was also broken down by tumour category (Table 13). Out of these tumour categories, patients diagnosed with CNS Tumours had the highest rate of Mortality Due to Malignancy.

Table 15: Mortality Due to Malignancy by Tumour Category

Tumour Category	**Deaths Due to Malignancy**	**Total Patients**	**Mortality Due to Malignancy (%)**	**95% CI**
CNS Tumour	24	43	55.8	41.0 - 70.7
GCT	52	703	7.4	5.5 - 9.3
Hepatoblastoma	19	42	45.2	30.2 - 60.3
Neuroblastoma	45	392	11.5	8.3 - 14.6
Other	3	27	11.1	-0.7 - 23.0
Renal Tumour	3	39	7.7	-0.7 - 16.1
Retinoblastoma	4	23	17.4	1.9 - 32.9
Soft Tissue Tumour	129	300	43	37.4 - 48.6

Figure 14: Mortality Due to Malignancy by Tumour Category (with 95% CI)



Pairwise comparisons were run to evaluate the differences between tumour categories for this outcome measure (see appendix). CNS Tumours had a statistically significant difference in the rate of Mortality Due to Malignancy from GCT ($p < 0.001$), Neuroblastomas ($p < 0.001$), Renal Tumours ($p < 0.001$), and tumours in the 'Other' category ($p = 0.005$). Additionally, GCT and Neuroblastomas differed significantly from CNS Tumours, Hepatoblastomas, and Soft Tissue Tumours (all $p < 0.001$). Due to perfect separation, a logistic regression failed. Fisher's exact test was used to determine the odds ratios for Mortality due to Malignancy by income level.

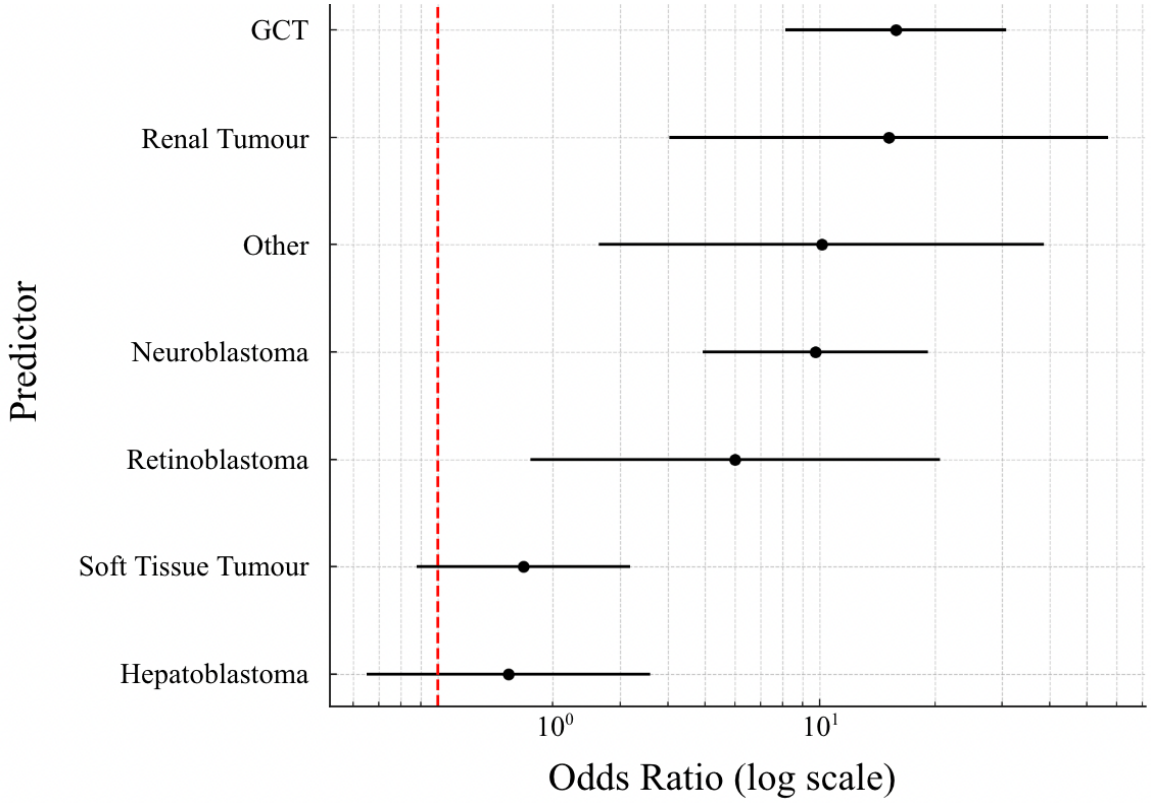
Table 16: Fisher's Exact Test Results for Mortality Due to Malignancy by Tumour Category

Tumour Category	**Odds Ratio (95% CI)**	**p-value**
Intercept (CNS Tumour)	1	—
Hepatoblastoma	1.53 (0.65-3.60)	0.33
Soft Tissue Tumour	1.67 (0.88-3.19)	0.11
Retinoblastoma	6 (1.75-20.62)	0.003

Neuroblastoma	9.74 (4.95-19.17)	< 0.001
Other	10.11 (2.64-38.70)	< 0.001
Renal Tumour	15.16 (4.04-56.90)	< 0.001
GCT	15.81 (8.13-30.75)	< 0.001

Figure 15 shows a forest plot depicting the odds ratios for Mortality Due to Malignancy by tumour category with confidence intervals. As the CNS Tumour group is the reference group, it is indicated at the baseline (odds ratio = 1.0 on the log scale).

Figure 15: Odds Ratios for Death due to Malignancy by Tumour Category



Preoperative Mortality

Across all studies, the overall preoperative mortality rate was determined to be 6.7%. Preoperative Mortality Rates were determined with respect to different income level countries (Table 17).

Table 17: Preoperative Mortality by Country Income Level

Country Income Level	Preoperative Deaths	Patients Intended for Surgery	Mortality Rate (%)	95% CI
High Income	91	1265	7.2	5.8 - 8.6
Upper Middle Income	10	159	6.3	2.5 - 10.1
Lower Middle Income	0	86	0.0	—
Total	101	1510	6.7	5.4 - 7.9

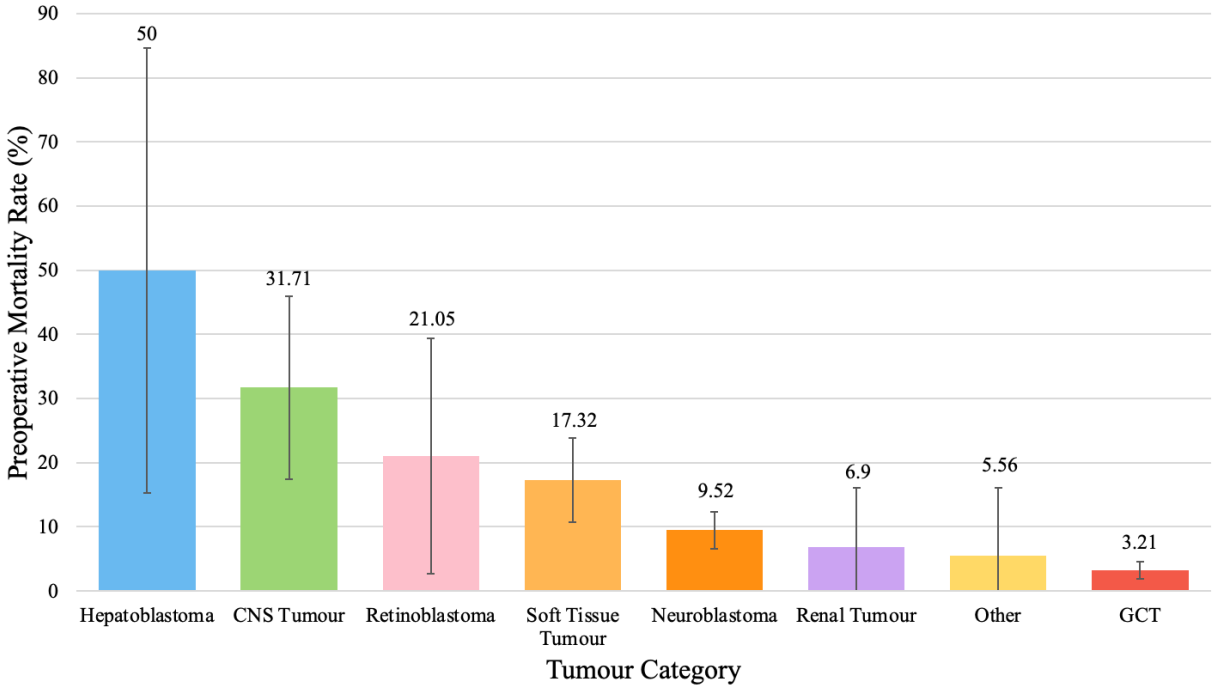
After running statistical comparisons between income levels using pairwise-Z tests, there was no statistically significant difference found between Preoperative Mortality rates in High Income and Upper Middle Income Countries (p=0.68).

Another sub analysis was run to determine the rates of Preoperative Mortality by tumour category (Table 18). The highest Preoperative Mortality rates were 50% for Hepatoblastoma and 31.7%, for CNS Tumour, though only 8 patients diagnosed with Hepatoblastomas were intended to receive surgery. The lowest rate of Preoperative Mortality, 3.2%, was for GCT, which had 686 patients who were intended to receive surgery.

Table 18: Preoperative Mortality by Tumour Category

Country Income Level	Preoperative Deaths	Patients Intended for Surgery	Mortality Rate (%)	95% CI
CNS Tumour	13	41	31.7	17.5 - 46
GCT	22	686	3.2	1.9 - 4.5
Hepatoblastoma	4	8	50	15.4 - 84.7
Neuroblastoma	38	399	9.5	6.6 - 12.4
Other	1	18	5.6	-5.0 - 16.1
Renal Tumour	2	29	6.9	-2.3 - 16.1
Retinoblastoma	4	19	21.1	2.7 - 39.4
Soft Tissue Tumour	22	127	17.3	10.7 - 23.9

Figure 16: Preoperative Mortality by Tumour Category (with 95% CI)



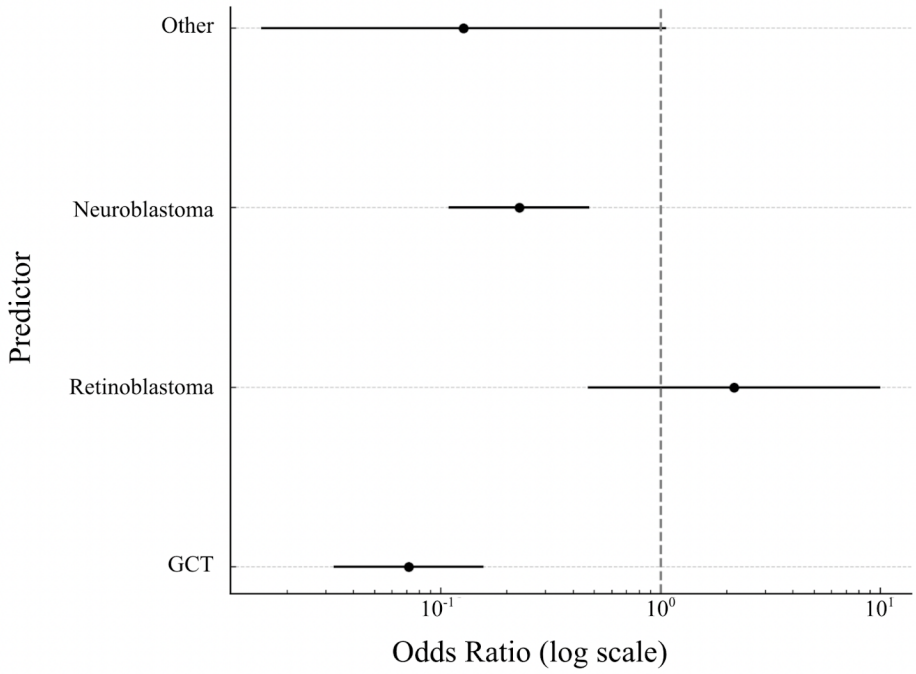
Pairwise comparisons (see appendix) between tumour categories for this outcome measure, reveal that Preoperative Mortality for CNS Tumour patients differs significantly from GCT and Neuroblastoma patients ($p<0.001$). GCT differs significantly from Hepatoblastoma ($p<0.001$), Neuroblastoma ($p<0.001$), Retinoblastoma ($p<0.05$), and Soft Tissue Tumours ($p<0.001$), while Neuroblastoma also differs significantly from Hepatoblastoma ($p<0.05$). A logistic regression was run to compare Preoperative Mortality by tumour category (GCT, Hepatoblastoma, and Neuroblastoma) using CNS Tumours as the intercept, (Table 19).

Table 19: Logistic Regression Results for Preoperative Mortality by Tumour Category

Tumour Category	**Coefficient**	**Odds Ratio (95% CI)**	**P-Value**
Intercept (CNS Tumour)	-0.77	0.46 (0.24-0.90)	0.02
GCT	-2.64	0.07 (0.03-0.16)	<0.001
Hepatoblastoma	0.77	2.15 (0.46-9.99)	0.33
Neuroblastoma	-1.48	0.23 (0.11-0.47)	<0.001

Figure 17 is a forest plot that depicts the odds ratios for Preoperative Mortality by tumour category with confidence intervals. As the CNS Tumour group is the reference group, it is indicated at the baseline (odds ratio = 1.0 on the log scale).

Figure 17: Odds Ratios for Preoperative Mortality by Tumour Category



Treatment Related Mortality

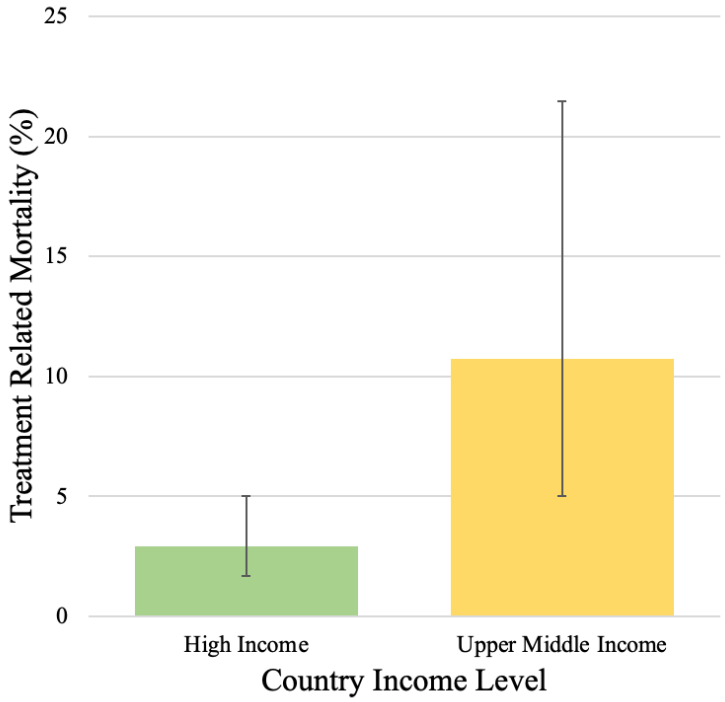
Across all studies, the overall Treatment Related Mortality rate was determined to be 3.9% (CI= 2.5% to 6.0%).

It was not possible to calculate a Treatment Related Mortality rate for Lower Middle Income Countries since no patients from these regions received chemotherapy or radiation.

Table 20: Treatment Related Mortality by Country Income Level

Country Income Level	Treatment Related Deaths	Patients Treated with SACT	Mortality Rate (%)	95% CI
High Income	12	412	2.9%	1.7 - 5.0
Upper Middle Income	6	56	10.7%	5.0 - 21.5
Lower Middle Income	0	0	—	—
Total	18	468	3.9%	2.5 - 6.0

Figure 18: Treatment Related Mortality by Country Income Level (with 95% CI)



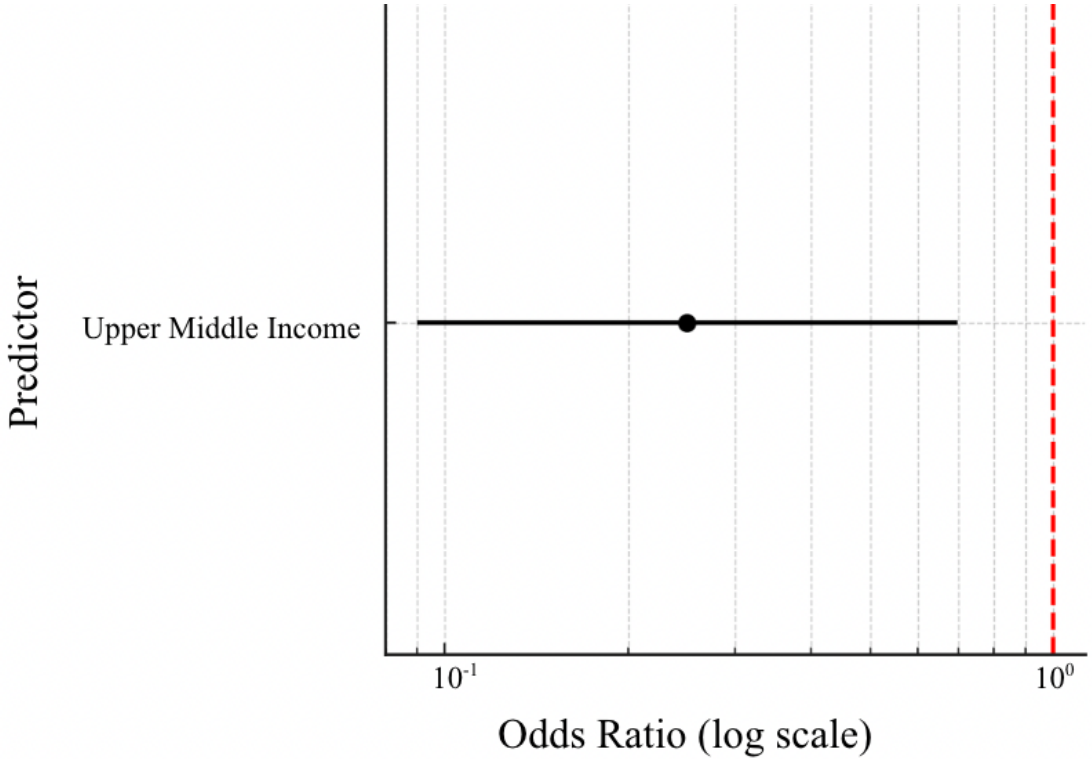
A pairwise test shows a statistically significant difference ($p < 0.05$) in Treatment Related Mortality rates between High Income Countries and Upper Middle Income Countries. Fisher's Exact test was used to determine the odds ratios for Treatment Related Mortality by income level.

Table 21: Fisher's Exact Test Result for Treatment Related Mortality by Country Income Level

Comparison	Odds Ratio	95% CI	p-value
Upper Middle vs High Income	0.25	0.09 - 0.70	0.004

Patients in High Income Countries had 75% lower odds of treatment related death than patients in Low Income Countries, and this difference is statistically significant ($p < 0.01$).

Figure 19: Odds Ratios for Treatment Related Mortality by Country Income Level



When broken down by tumour category, though differences in Treatment Related Mortality rates were observed, sample sizes were much smaller than for other measures. Pairwise statistical comparisons revealed no statistically significant differences (see appendix).

Table 22: Treatment Related Mortality by Tumour Category

Tumour Category	Treatment Related Deaths	Patients Treated with SACT	Mortality Rate (%)	95% CI
CNS Tumour	0	8	0	—
GCT	2	151	1.32	0 - 3.2
Hepatoblastoma	1	7	14.29	0 - 40.2
Neuroblastoma	10	145	6.9	2.8 - 11.0
Other	0	7	0	—
Renal Tumour	1	14	7.14	0 - 20.6
Retinoblastoma	0	29	0	—
Soft Tissue Tumour	2	63	3.17	0 - 7.5

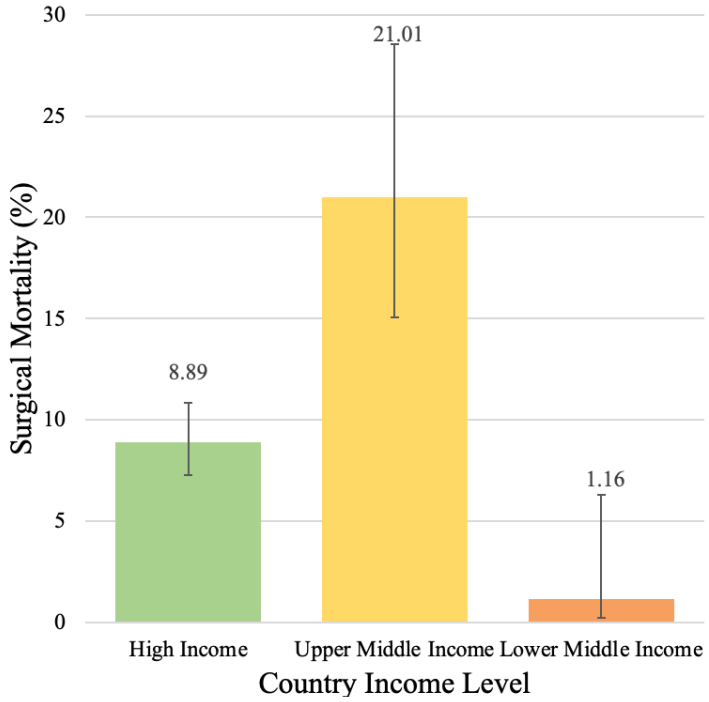
Surgical Mortality

Across all studies, the overall Surgical Mortality Rate was determined to be 9.7%. When broken down by country income level (Table 23, Figure 20), High Income Countries had a 8.9% Surgical Mortality Rate, while Upper Middle Income Countries had 21%. The only death in the sample of 86 patients from Lower Middle Income Countries occurred during surgical intervention, resulting in a Surgical Mortality Rate of 1.2%.

Table 23: Surgical Mortality by Country Income Level

Country Income Level	Deaths Due to Surgery	Patients Receiving Surgery	Mortality Rate (%)	95% CI
High Income	88	990	8.9	7.3 - 10.8
Upper Middle Income	29	138	21.0	15.1 - 28.6
Lower Middle Income	1	86	1.2	0.2 - 6.3
Total	118	1214	9.7	8.2 - 11.5

Figure 20: Surgical Mortality by Country Income Level (with 95% CI)



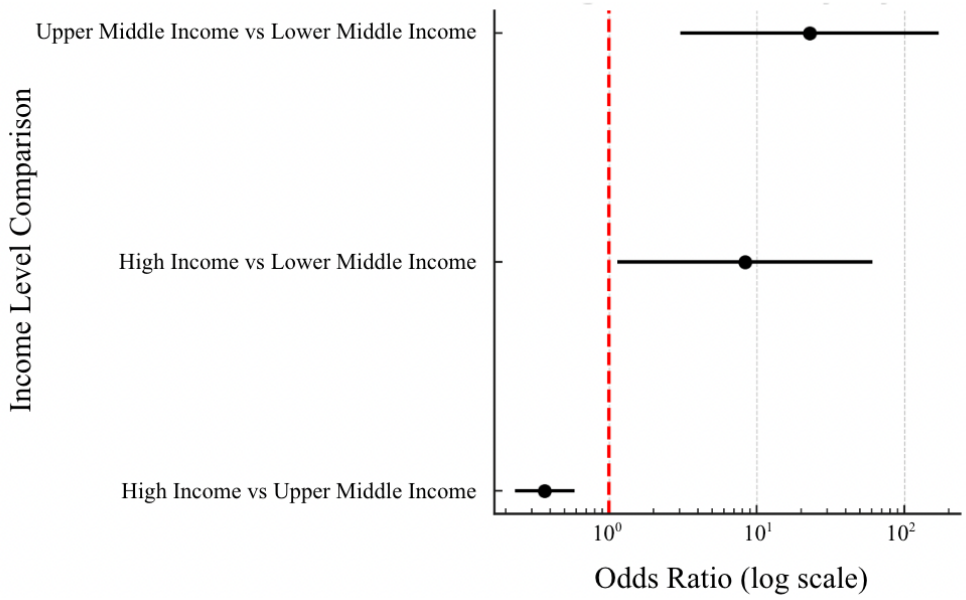
The pairwise-Z tests (see appendix) show significant differences in Surgical Mortality rates between income levels, even with the Bonferroni correction applied ($p<0.05$). Fisher's Exact test was used to determine the odds ratios for Surgical Mortality by income level.

Table 24: Fisher's Exact Test Results for Surgical Mortality by Country Income Level

Comparison	Odds Ratio	95% CI	p-value
High Income vs Upper Middle Income	0.37	0.2 - 0.5	<0.001
High Income vs Lower Middle Income	8.30	1.1 - 60.3	0.01
Upper Middle Income vs Lower Middle Income	22.61	3.0 - 169.4	<0.001

This analysis suggests that patients in Upper Middle Income Countries had 63.3% higher odds of death due to surgical intervention than patients in High Income Countries, and this is statistically significant ($p < 0.01$). For Figure 21, the red line indicates no difference between the groups. Results to the left of the red line are suggestive of lower mortality odds in the first group listed. Results to the right represent higher mortality odds.

Figure 21: Odds Ratios for Surgical Mortality by Country Income Level



When rate of Surgical Mortality is analysed by tumour category, pairwise tests show only significant differences for Hepatoblastoma after multiple comparison correction (see appendix). Due to the small sample size for Hepatoblastoma, logistic regression was not conducted.

Table 25: Surgical Mortality by Tumour Category

Tumour Category	Deaths Due to Surgery	Patients Receiving Surgery	Mortality Rate (%)	95% CI
CNS Tumour	2	6	33.3	0 - 71.1
GCT	53	607	8.7	6.5 - 11.0
Hepatoblastoma	18	28	64.3	46.5 - 82.0
Neuroblastoma	19	244	7.8	4.4 - 11.2
Other	1	28	3.6	0 - 10.5
Renal Tumour	1	26	3.9	0 - 11.2
Retinoblastoma	0	15	0	—
Soft Tissue Tumour	23	176	13.1	8.1 - 18.1

Mortality Due to Metastasis

Across all studies, the mortality due to metastasis was determined to be 4.5%. Table 26 shows this measure broken down by country income level. After running a pairwise comparison, none of these differ significantly from the others ($p>0.05$) (see appendix).

Table 26: Mortality Due to Metastasis by Country Income Level

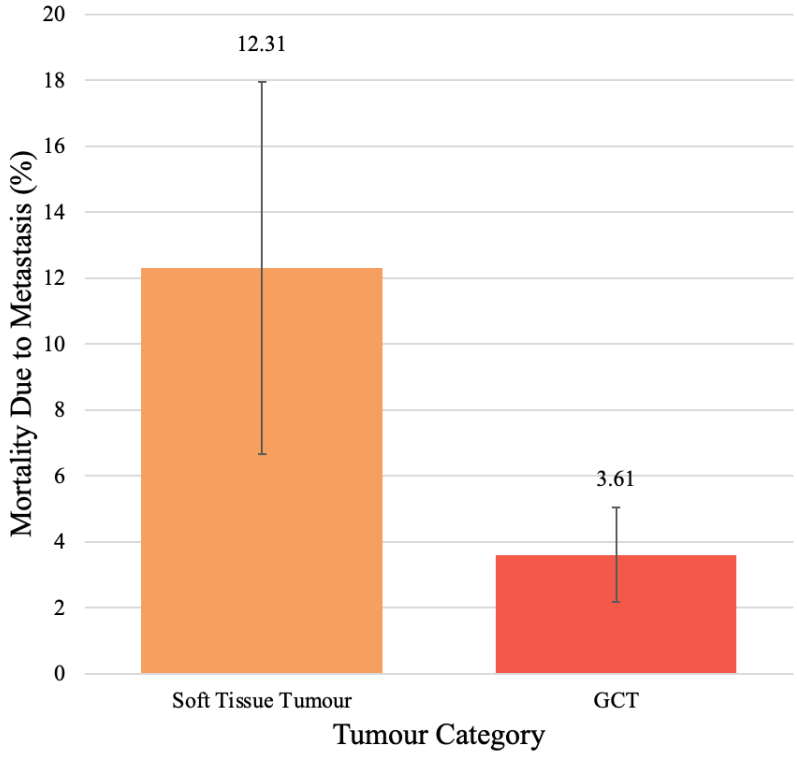
Country Income Level	Deaths due to Metastatic Disease	Total Patients	Mortality Rate (%)	95% CI
High Income	50	1085	4.6	3.4 - 5.9
Upper Middle Income	11	178	6.2	2.6 - 9.7
Lower Middle Income	0	86	0	—
Total	61	1349	4.5	3.4 - 5.6

A similar analysis was run between rates of mortality due to metastasis for different tumour categories. The only statistically significant difference ($p<0.001$) that was identified was between Soft Tissue Tumours (12.3%) and Germ Cell Tumours (3.6%) (see appendix).

Table 27: Mortality Due to Metastasis by Tumour Category

Tumour Category	Deaths due to Metastatic Disease	Total Patients	Mortality Rate (%)	95% CI
CNS Tumour	0	14	0	—
GCT	24	665	3.6	2.2 - 5.0
Hepatoblastoma	1	10	10	0 - 28.6
Neuroblastoma	17	369	4.6	2.5 - 6.8
Other	1	33	3.0	0 - 8.9
Renal Tumour	1	34	2.9	0 - 8.6
Retinoblastoma	0	20	0	—
Soft Tissue Tumour	16	130	12.3	6.7 - 18.0
Total	60	1275	4.7	3.5 - 5.9

Figure 22: Mortality Due to Metastasis by Tumour Category (with 95% CI)



Fisher's Exact Test yields a 0.27 Odds Ratio for Soft Tissue Tumour vs GCT, suggesting that patients diagnosed with Soft Tissue Tumours are 3.75 times more likely to die from disease progression than patients diagnosed with GCTs.

Table 28: Fisher's Exact Test for Mortality Due to Metastasis by Tumour Category

Comparison	Odds Ratio	95% CI	p-value
Soft Tissue Tumour vs GCT	0.27	0.1 - 0.5	<0.001

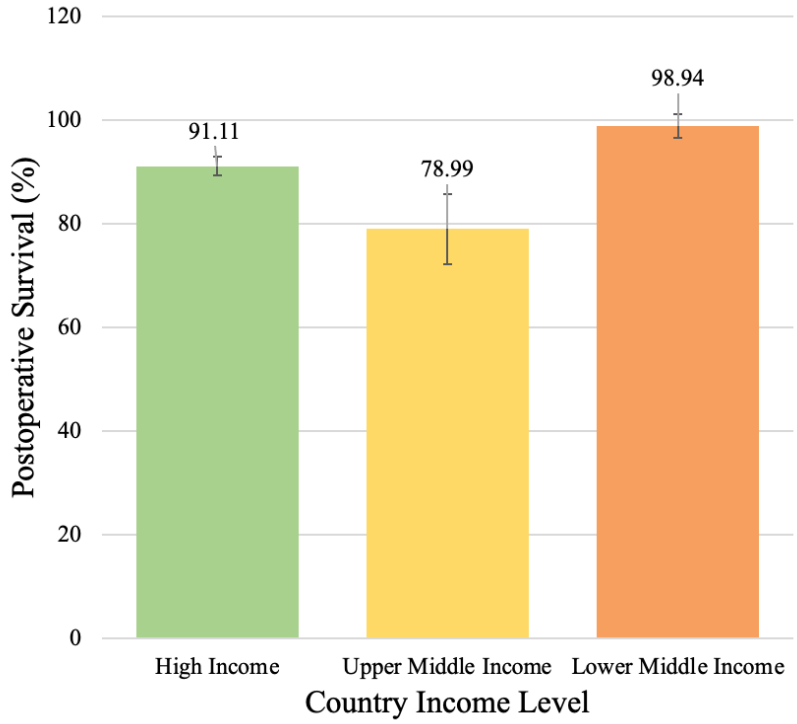
Postoperative Survival

Across all studies, the overall postoperative survival rate was determined to be 90.3%

Table 29: Postoperative Survival Rate by Country Income Level

Country Income Level	Patients Surviving Surgery	Patients Receiving Surgery	Survival Rate (%)	95% CI
High Income	902	990	91.1	89.3 - 92.9
Upper Middle Income	109	138	79.0	72.2 - 85.8
Lower Middle Income	85	86	98.8	96.6 - 101.1
Total	1096	1214	90.3	88.6 - 91.9

Figure 23: Postoperative Survival by Tumour Category (with 95% CI)



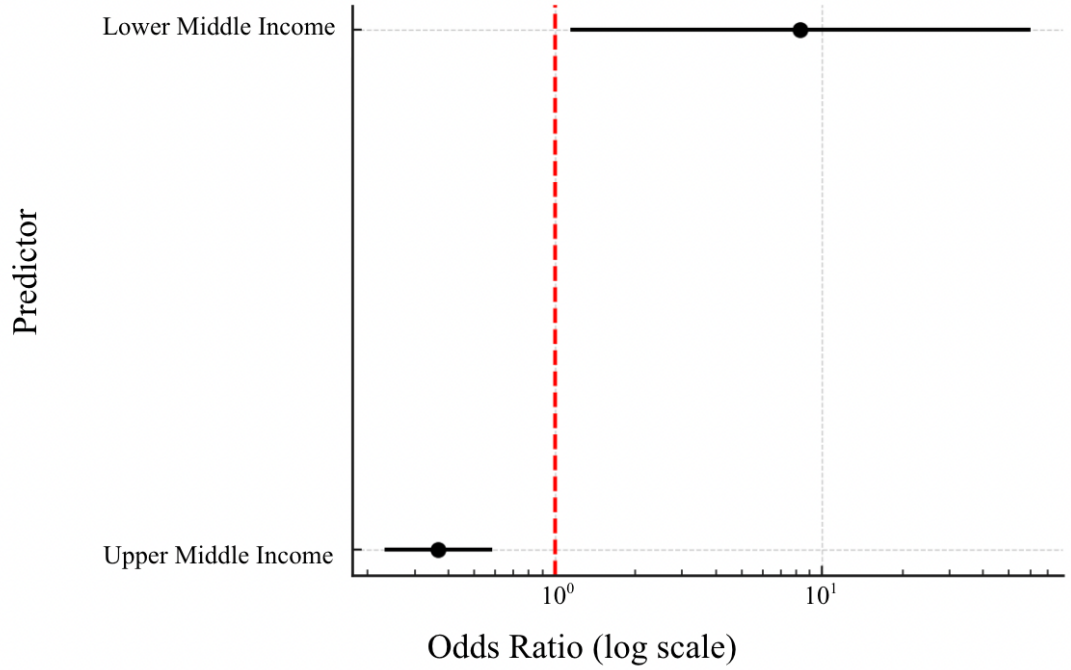
Pairwise comparisons find highly statistically significant differences between High Income and Upper Middle Income Countries and Upper Middle Income Countries and Lower Middle Income Countries ($p<0.001$), and a statistically significant difference between High Income and Lower Middle Income Countries ($p<0.05$).

A logistic regression reveals the odds of postoperative survival are significantly lower ($p<0.001$) for Upper Middle Income Countries than High Income Countries. Patients in High Income Countries are 63% more likely to survive surgical intervention than patients in Upper Middle Income Countries (Odds Ratio: 0.37). The odds of Postoperative Survival are higher ($p<0.05$) for Lower Middle Income Countries than High Income Countries. Patients in Low Income Countries are 8 times more likely to survive surgical intervention than patients in High Income Countries (Odds Ratio: 8.29).

Table 30: Logistic Regression for Postoperative Survival Rate by Country Income Level

Country Income Level	Coefficient	Odds Ratio	95% CI	P-Value
Intercept (High Income)	2.33	10.25	8.2 - 12.8	<0.001
Upper Middle Income	-1.00	0.37	0.2 - 0.6	<0.001
Lower Middle Income	2.12	8.29	1.1 - 60.3	0.04

Figure 24: Odds Ratios for Postoperative Survival by Country Income Level



Similar to Surgical Mortality, when Postoperative Survival is analysed by tumour category, pairwise tests show statistically significant differences for Hepatoblastoma after correcting for multiple comparisons (see appendix). Due to the small sample size for Hepatoblastomas a logistic regression was not conducted.

Table 31: Postoperative Survival Rate by Country Income Level

Tumour Category	Patients Surviving Surgery	Patients Receiving Surgery	Survival Rate (%)	95% CI
CNS Tumour	4	6	66.7	29.0 - 100
GCT	554	607	91.3	89.0 - 93.5
Hepatoblastoma	10	28	35.7	18.0 - 53.5
Neuroblastoma	225	244	92.2	88.9 - 95.6
Other	17	28	60.7	42.6 - 78.8
Renal Tumour	25	26	96.2	88.8 - 100.0
Retinoblastoma	15	15	100	—
Soft Tissue Tumour	153	176	86.9	82.0 - 91.9
Overall	1003	1130	88.8	86.9 - 90.6

2.4 Discussion

2.4.1 The Method: Strengths and Limitations

The search strategy as documented in the Methods was applied to three databases, which provided a broad scope of literature. Though comprehensive, this search could have been expanded to a larger set of databases to further reduce publication bias. The search utilized the widely used structure of PICO (Population: neonatal tumour patients, Intervention: surgical treatment in HICs, Comparison: surgical treatment in LMICs, and Outcome: mortality and survival). As we were searching for data in both HICs and LMICs, we did not include a term for country income level, but all other terms were included in our search as both free-text terms (set to title, abstract, and keyword settings) and MeSH terms as per guidelines published by Tawfik, et. al, in 2019. For each free-text term, various spellings and iterations of the term were included. For example, searching tumo?r* captures ‘tumor,’ ‘tumour,’ and the plurals of these, and the search ‘infant OR neonate OR newborn’ ensures that we capture all literature relevant to our population. With no language or publication date limits, our search cast a wide net. One limitation to this, however, is that it allowed for much more heterogeneity in data formatting and reporting methods, especially in earlier publications.

2.4.2 Heterogeneity in the Reporting of the Data

In terms of study quality, ideally there would be a more even distribution of low bias studies across country income levels. 9 out of the 10 low bias studies were from HICs. Out of the studies from Lower Middle Income Countries, all three had a moderate risk of bias: two studies rated 5/9 stars and one rated 6/9 stars. For studies from Upper Middle Income Countries, three had a moderate risk of bias (rated 6/9 stars) and one had a low risk of bias (rated 7/9 stars).

Heterogeneity in our meta-analysis is sizable, though our leave-one out analysis demonstrated that no one study had a significantly greater impact on survival rate than the rest. Even though we had to apply a continuity correction to mitigate the effects of the two studies with 100% survival rate (zero variance), these studies did not disproportionately impact the pooled survival rate because of their small sample sizes. Both are from Lower Middle Income Countries and almost certainly are representative of a publication bias for publishing positive outcomes. This deduction is supported by the fact that the subgroup-specific pooled survival rates, demonstrated extreme differences in heterogeneity by country income level. Within subgroups, while the High Income and Upper Middle Income Country groups had I^2 values of 86.9% and 88.5% respectively (suggesting high heterogeneity), Lower Middle Income Countries had an I^2 value of 0, which suggests there was no heterogeneity between studies. This was also demonstrated in the DerSimonian-Laird subgroup analysis for which Lower Middle Income Countries showed very high survival with 0 variance ($Tau^2 = 0$).

In terms of data collection, we were limited by inconsistent reporting methods as aforementioned. For example, in terms of our measure of 'Overall Survival,' there was a lack of consistency in how follow-up was reported, particularly pertaining to age at follow-up, reporting event-free survival, etc. Some studies did not report an age whatsoever at follow up. Others reported survival at a specific age (e.g., 5-year survival rate). Even more troublesome were studies that reported follow up differently for each patient. For example, the first study we recorded data for, Gundry et. al, 1983, reports on each individual patient diagnosed with cervical teratomas at one hospital over an 8-year span of time. For one patient, this study reports, 'One year following the procedure the patient was doing well with no evidence of recurrence or metastases,' though for another they write, 'The patient had an uneventful postoperative recovery

and is well at 4 years of age.' With such variability in reporting, even within individual studies, we elected to report an 'Overall Survival' instead of survival at a certain age.

This variability in reporting was also noted in how studies reported demographics, diagnosis, and interventions. For 41.3% of patients (n = 835) sex was not reported, and for 20.1% of patients (n = 407) the time period of diagnosis was not reported. Perhaps more importantly, we were unable to report interventions separately in terms of the number of patients receiving only one treatment (surgical intervention or chemotherapy/radiation) separate from the number receiving multiple treatments. With only 24 studies containing separable statistics for interventions, we were unable to truly grasp the proportion of surgical vs other treatment for Neonatal Tumours, much less by income level or tumour category. Such a measure has yet to be estimated, and with these malignancies posing a unique treatment dilemma this information is crucial to our understanding of Neonatal Tumour management.

Finally, there were significant discrepancies in which countries had published data at all. As it stands, this review elucidates the extreme lack of reporting from LMICs. We have virtually no representative data or results on the types, management, or outcomes of Neonatal Tumours in low income regions of the world, as not a single study that matched our inclusion criteria came from a true Low Income Country. Only 3 studies from Lower Middle Income Countries matched our inclusion criteria, and all three of these were conducted in tertiary care medical colleges in urban centres in northern India: Rohtak (44 patients), Chandigarh (32 patients), and New Delhi (10 patients). This draws attention to two important considerations, the first of which is that findings made in India cannot be representative of the data we might see in other Lower Middle Income Countries. India is the most populous country in the world, and due to the sheer volume of surgery that medical practitioners provide, this experience and expertise might account for the high survival outcomes we see in this literature. The second point is that the data that has been collected from LMICs seems to come from urban centres which have a higher quality of care and a larger quantity of specialized physicians who have the capacity and training to address management of Neonatal Tumours. The patient population that receives treatment in urban centres often has the means to either live in these areas or afford the travel to access specialized services there. On the contrary, a large percentage of the population in LMICs live in rural

regions with significantly less access to the specialized care required to treat these complex malignancies. One study in 2009 found that 74% of doctors in India live in urban areas, serving only 28% of the population, while in rural areas Primary Health Centres and Community Health Centres are lacking 8% and 65% of medical staffing respectively at the time (Kapil et al., 2009). Due to this lack of accessibility to treatment and staffing shortages, data on the treatment and outcomes in this population goes almost entirely unreported. Therefore, we are effectively comparing between outcomes for patients in HICs and their higher income counterparts in LMICs, leaving the less affluent majority of the LMIC patient population unaccounted for.

2.4.3 Patient Characteristics and Primary Outcomes

Within the 8 identified tumour categories, 39.3% (n = 796) of tumours diagnosed in our study population were GCT. This was followed by Neuroblastomas at 28.9% (n = 584) and Soft Tissue Tumours 18% (n = 364). GCT were the most diagnosed tumours across all income levels, making up 84.9% of tumours from Lower Middle Income Countries, 36.0% of tumours from Upper Middle Income Countries, and 37.6% of tumours from High Income Countries. We can note that two out of the three published reviews from Lower Middle Income Countries included in our study were specifically reviewing Neonatal Sacrococcygeal Teratoma, which happens to be the most prevalent type of GCT found in our study (n = 532), and is reported to be the 'most common solid tumour in newborn infants' (Yoon et. al, 2018). This information also makes the high survival rate in Lower Middle Income Countries seem slightly more reasonable, given the fact that patients diagnosed with GCT had statistically better survival than most other tumour categories.

As expected, our data showed a trend of antenatal diagnosis increasing and postnatal diagnosis decreasing over time. Additionally, HICs had the highest rates of antenatal diagnosis, and country income level was found to be a statistically significant predictor of antenatal vs postnatal diagnosis rates. However, we must remember that the small sample size for our Lower Middle Income Country category leads to unreliable statistics that cannot be truly representative of neonatal tumour management and outcomes in these countries. With 75.7% of patients (n=1531) receiving surgical intervention, we can confirm that surgery was the mainstay of treatment for patients within our dataset.

Across these studies we calculated an overall survival rate of 79.3%, which is a relatively high. This is likely because Neonatal Tumours have a good biology. One study reports that 84.3% of Neonatal Tumours are benign (Chandrasekaran, 2018). They often have histologic presentations of low mitotic rate, sarcomatous appearance, and densely arranged cells. These characteristics make most neonatal tumours relatively straightforward to treat through surgical resection (aside from complications during birth, difficulties with adjuvant/neoadjuvant treatment, and other impediments that have been previously mentioned).

We found that HICs had a higher survival rate (79.1%) than Upper Middle Income Countries (71.9%) and that this difference was statistically significant. With an odds ratio of 0.68, this means that survival in Upper Middle Income Countries was 32% less likely than in High Income Countries. In contrast, there was only one observed death in our Lower Middle Income group, yielding an unreasonably high survival rate of 98.8%. The odds of survival for patients with neonatal tumours in Lower Middle Income Countries was 22.5 times higher than in High Income Countries. The extremely wide confidence intervals seen in Figure 11 for this statistic are reflective of the small sample size in Lower Middle Income Countries and increase concerns about statistical stability, precision, and representativeness. This survival rate and odds ratio reinforce our conjecture that there is some publication bias at play. We must consider the fact that only good outcomes are being reported in Lower Middle Income Countries, which is an extremely concerning notion given the already lacking body of research on this subject.

When considering survival by tumour category, we find that GCTs and Neuroblastomas had statistically better survival than most other tumour categories. On the other hand, CNS Tumours had statistically worse survival than almost all tumour categories at 43.8%, though we again must note the small sample size of 79 patients. GCT and Neuroblastoma patients had 9.18 and 6.22 times higher odds of survival than CNS tumour patients respectively. CNS Tumour survival rate in the general paediatrics population is reportedly 65.3% as per a recent population-based study (Hossain et. al, 2021) analysing a database containing 15,723 cases. Patients were sorted into age groups of <1 year, 1-9 years, and 10-19 years. This study emphasized the fact that ‘mortality risk declined with increased age at diagnosis.’ Notably, survival for patients less than 1 year of age was 54.7% which was much closer to our noted survival (Hossain et. al, 2021). To

answer the question of why survival for CNS Tumours is so much worse in the neonatal population, we must look at differences in treatment. Even within adult CNS Tumour patients, the 'standard of care is a combination of radiotherapy and chemotherapy' due to the fact that brain or spinal surgery can be extremely invasive, high-risk, and not always successful in removing the entire tumour, and this risk is only exacerbated in neonates (van de Bent et al., 2023). Studies that evaluate chemotherapy as a treatment option in neonates note excess rates of toxicity. One author reasons that for neonates, 'dose regimens are generally not evidence based, and dosing strategies are frequently inconsistent between tumour types and treatment protocols,' (Nijstad et. al, 2022). In our study, of the 6 reviews containing information about CNS Tumours, only 6 out of 79 patients were reported to receive surgery and 8 were treated with chemotherapy. Additionally, out of the 3 studies reporting on both CNS tumour patients and conservative management, 16 of 44 CNS tumour patients were managed conservatively.

2.4.4 The Odds Ratios for the Association Between Outcome Measures and Country Income Level

Three outcome measures were found to differ significantly by country income level. These are Treatment Related Mortality, Surgical Mortality, and Postoperative Survival.

In the largest single centre study reporting mortality outcomes in patients over 16 years of age within 30 days of Systemic Anti-Cancer Therapy (SACT), Treatment Related Mortality was only 0.44% (Khoja et. al, 2015). In our study, the overall Treatment Related Mortality rate was found to be 3.9%, which further emphasizes how much more susceptible neonates are to SACT. Treatment Related Mortality for Neonatal Tumours is much lower for High Income Countries (2.9%) than Upper Middle Income Countries (10.7%), though we must note that only 56 patients in Upper Middle Income Countries received SACT compared to 412 patients in High Income Countries. Patients in Upper Middle Income countries were 75% more likely to die from SACT than patients in High Income Countries. Interestingly, 0 patients from Lower Middle Income Countries were treated with SACT. One review investigating affordability and access to anti-cancer medicines in LMICs provides some insight into this disparity, concluding that barriers to SACT include high cost, limited public insurance coverage, and limited or non-existent availability of these treatments at facilities in low income regions (Ocran Mattila et al., 2021).

Overall Surgical Mortality and Postoperative Survival rates reveal the same conclusions. Surgical Mortality in our study was found to be 9.7% and Postoperative Survival was 90.3%. High Income Countries had a staggeringly lower rate of Surgical Mortality at 8.9% as compared to Upper Middle Income Countries at 21.0%. With only one reported death, Lower Middle Income Countries had the lowest rate of surgical mortality at 1.2%. Patients in Upper Middle Income Countries had 63.3% higher odds of death during or immediately following surgical intervention than patients in High Income Countries, and patients from Lower Middle Income Countries were 8 times less likely than patients in High Income Countries to die from this cause. Once again, these statistics call into question the representativeness of our sample and suggest a strong publication bias.

2.4.5 The Odds Ratios for the Association Between Outcome Measures and Tumour Type

Three outcome measures were found to differ significantly by tumour type. These are Mortality Due to Malignancy, Preoperative Mortality, and Mortality Due to Metastasis.

Overall Mortality Due to Malignancy was found to be 12.9%, though patients diagnosed with CNS Tumours had a much higher rate of Mortality Due to Malignancy at 55.8%. Patients with the lowest odds of Mortality Due to Malignancy compared to CNS Tumour patients were GCT patients who were 15.81 times less likely to succumb to the disease. This difference can be accounted for by the fact that a common type of GCT, Sacrococcygeal Teratoma, is known to be very treatable in children. One study investigating outcomes of Paediatric Sacrococcygeal Teratoma found survival to be 95% (Yadav et al., 2020). This diagnosis constitutes 66.8% of the GCT that were diagnosed in our study, therefore it is logical that GCT mortality is the lowest out of all tumour categories in our dataset at 7.4%.

In a similar fashion, while overall Preoperative Mortality in our study was found to be 6.7%, in CNS Tumours this was found to be 31.7%. Compared to GCT which had the lowest Preoperative Mortality at 3.2%, this leaves CNS Tumour patients 97% more likely to succumb to the disease before possible intervention. This estimate is likely extreme given the only 41 CNS Tumour patients with data for this measure, though the finding continues to support the conclusion that

CNS Tumours are more aggressive and difficult to treat than other types of tumours in neonates.

The final measure to discuss, Mortality Due to Metastasis, was found to be 4.5% overall in our study. Only 14 CNS Tumour patients had data reported for this measure, and 0 deaths occurred due to metastasis of the cancer. Once again, GCT patients had the lowest rate of mortality for this measure at 3.6%, while Soft Tissue Tumour patients had the highest rate of mortality at 12.3%. Therefore, Soft Tissue Tumour patients were 3.75 times more likely to die from disease progression than GCT patients. In adults, estimated overall 5-year survival for Soft Tissue Sarcomas is 50% (Kaye et. al, 2018). One study suggests that one reason for the low survival rate is that these sarcomas tend to be extremely vascular, posing a surgical challenge. This challenge is likely exacerbated in neonates due to the already complex nature of surgical intervention in this population. A 'high proportion of patients with metastases' is also reported in the literature for this tumour category with common sites of metastases occurring in the lungs and liver (Kaye et. al, 2018).

2.4.6 Contribution to the Field

If this systematic review makes one thing evident, it is the fact that there really is a very limited body of existing literature on Neonatal Tumours. This is even smaller in LMICs, and with the strong publication bias observed for Neonatal Tumour data in LMICs, there is little information to draw conclusions from that might help for the future standardization of the management of this disease in these regions of the world.

That being said, this review provides insight into the gaps in this body of literature. To the best of our ability, we have compiled and coalesced a broad range of data to compare how types of tumours and interventions differ between HICs and LMICs and how these varying factors impact survival outcomes in neonates. Interestingly, all measures related to treatment provision and outcomes (Treatment Related Mortality, Surgical Mortality, and Postoperative Survival) were found to differ significantly by country income level, while all measures related to the progression of the disease and unrelated to intervention (Mortality Due to Malignancy, Preoperative Mortality, and Mortality Due to Metastasis) all differed significantly by tumour

type. This is suggestive that management and treatment of Neonatal Tumours differ by income level and have significant impacts on survival outcomes. Alternatively, for measures that are less dependent on interventions, such as death prior to any possible intervention, the type of Neonatal Tumour dictates survival odds. Though further studies and a higher quantity of data are needed to confirm these conclusions, we hope that this systematic review will provide evidence and motivation for increased reporting and more standardized management of Neonatal Tumours in countries across the globe.

Chapter 3: Making the Case for Case Reports: A Review of Grey Literature and a Novel System of Categorization with a Focus on Neonatal Tumours

3.1 Subject of the Review

Review Title: Making the Case for Case Reports: A Review of Grey Literature and a Novel System of Categorization with a Focus on Neonatal Tumours

Review Questions:

1) What does grey literature reveal about types of neonatal Tumours and care practices between different country income levels?
2) Can case reports be categorized by their content to better organize grey literature and increase our understanding of their significance in scientific literature?

3.2 Methods

3.2.1 Search Strategy and Study Screening

The same search strategy from the systematic review was employed for this study using the three OVID databases: Medline, Embase, and Global Health. Terms pertaining to tumours, neonates, surgery, and outcome measures were adapted for use between each database using database-specific filters (See Table 1 in Chapter 2.2.1). There was no restriction on publication date for study selection. Deduplication was performed using Endnote, and Screening was then performed in Rayyan. Studies that were selected were all Case Reports that had been screened out of the systematic review. Retrieved studies were screened independently by two reviewers (LB and FL). The titles and/or abstracts of these studies were reviewed to identify studies meeting the inclusion criteria. Discrepancies were resolved through discussion and consultation of a third reviewer (NK). For studies which were accepted through this screening process, full texts were assessed for eligibility by the two screeners, with discrepancies being resolved in the same manner. Articles that fulfilled all inclusion criteria were used for the final review.

3.2.2 Inclusion and Exclusion Criteria

The patients included in this study were aged 0 to 28 days – per the definition of 'neonate' used by the World Health Organization – with a documented diagnosis of a Neonatal Tumour. Patients who were antenatally diagnosed with in-utero management reported were included as well, under the stipulation that they survived to birth and were managed postnatally as well. For cases in which patients were diagnosed within the 0-28 day period but treated after this period, or for which symptoms arose during this age and the patient was diagnosed after this period, these reports were also included in the study. Case reports and case series were included, while studies using consecutive or retrospective sampling were excluded along with review articles, opinion pieces, case-control studies, cross-sectional studies, cohort studies, and randomized control trials. There were no publication date or language limits.

3.2.3 Data Extraction

Data was extracted from the accepted studies using a pre-piloted, standardised Excel sheet. Two reviewers completed data extraction, and a third reviewer resolved discrepancies when necessary. The following data was extracted from these articles for each reported case: year of publication, title, country where patients were treated, sex of patient, type of tumour, time period of diagnosis (antenatal or postnatal), age at diagnosis (week of gestation or postnatal age), diagnostic examinations received, interventions received, age at surgical intervention, and outcome. Separately, quotes were extracted from each report to be analysed for categorization within data analysis.

3.2.4 Critical Appraisal (Case Report Quality) Assessment

The Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Reports was used to assess the quality of each case report. Each article was assessed independently by two reviewers. These results were then compared and discrepancies were resolved through agreement or consultation of a third reviewer. For this assessment, 8 criteria were evaluated for each case report:

1. Were the patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?

4. Were diagnostic tests or methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

For each evaluation, possible answers were Yes, No, or Not Applicable (NA). After this checklist had been completed and scored out of 8, reviewers discussed whether or not the case report should be included in the study.

3.2.5 Data Synthesis and Qualitative Analysis

An assessment of statistical heterogeneity was not conducted as this review dealt with individual cases and mostly focused on a qualitative analysis with limited generalizability (not a meta-analysis). For these reasons, quantitative statistical analysis was not feasible for the data that was collected. However, we reported observations on tumour types, demographics, diagnostics, treatment, and survival. For categorical variables, such as patient sex or period of diagnosis, data from all reports were summed as percentages. Specifically, we reported observations broken down into subgroups of country income levels and tumour categories. World Bank definitions were used to categorize countries as Low Income Countries, Lower Middle Income Countries, Upper Middle Income Countries, and High Income Countries. Whenever Low-Middle Income Countries are referred to (LMICs), this is the grouping of Low, Lower Middle, and Upper Middle Income Countries into one category. Country income level status was determined using the 2024-2025 World Bank Atlas GNI per capita method.

A thematic analysis was then conducted to categorize case reports by their main subject of focus. Two reviewers analysed the titles, abstracts, and full texts of all 71 reports and extracted themes. Discussion between reviewers confirmed the coding index that would be utilized, organizing themes into a larger framework of categories (Figure __). For each category, themes explain what case reports within this category intend to present and the main purpose that reports in this category serve. The thematic analysis included multiple rigorous rounds of data review, during which each report was assigned themes and corresponding categories by each reviewer. These decisions were compared, and discrepancies were resolved by a third reviewer.

Table 32: Framework for Case Report Categories and Themes

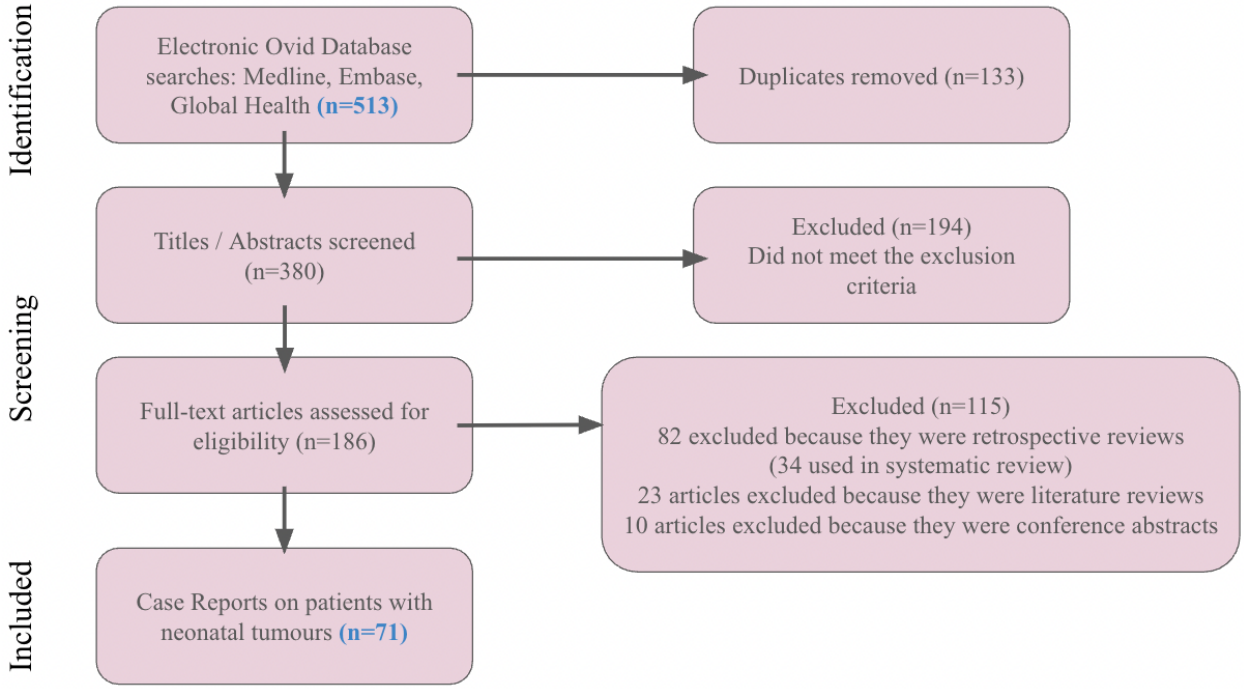
Category	Themes
Management	1. Advocating the use of a technique or treatment 2. Failures or successes in treatment 3. Recommend standardization of perioperative practices 4. Treatment of an unusual case Purpose: To report suggestions or dilemmas in treatment of a case for future consideration of care practices.
Diagnostics	1. Advocating [early] detection (e.g. prenatal screening, new screening tools, etc). 2. Failures or successes in diagnosis 3. Emphasizing or presenting diagnostic markers 4. Avoiding misdiagnosis 5. Clarifying differential diagnosis Purpose: To report suggestions or dilemmas in diagnosis of a case for future consideration of care practices.
Unique Presentation	1. Uncommon features (e.g. symptoms, comorbidities, associations, locations) Purpose: To bring attention to a specific phenotype / presentation of the disease that might not be easily recognized.
Rare Case	1. First documented case of specific diagnosis in population of interest (i.e. neonates with tumours) a. In a demographic group (e.g. race, sex, age) b. In a patient population (e.g. premature infant, cancer patient, fetus) c. In a location (e.g. South Africa) Purpose: To document a landmark case, specifically when it is the first of its kind in the literature.
Etiology / Pathogenesis	1. Considering the cause of the disease (e.g. genetic factors, environmental factors, epigenetic factors, etc.) 2. Considering the how a specific phenotype/subset of the disease arises Purpose: To propose investigation into a particular origin of / contributing factor to the disease.

3.3 Results

3.3.1 Report Search and Report Characteristics

The initial literature search that was conducted resulted in 513 articles. 133 duplicates were removed. 380 articles underwent title and abstract screening. 186 articles underwent full text screening, and 71 articles met the inclusion criteria and were included in the final review (Figure 24). All of these were Case Reports.

Figure 25: Prisma Flowchart



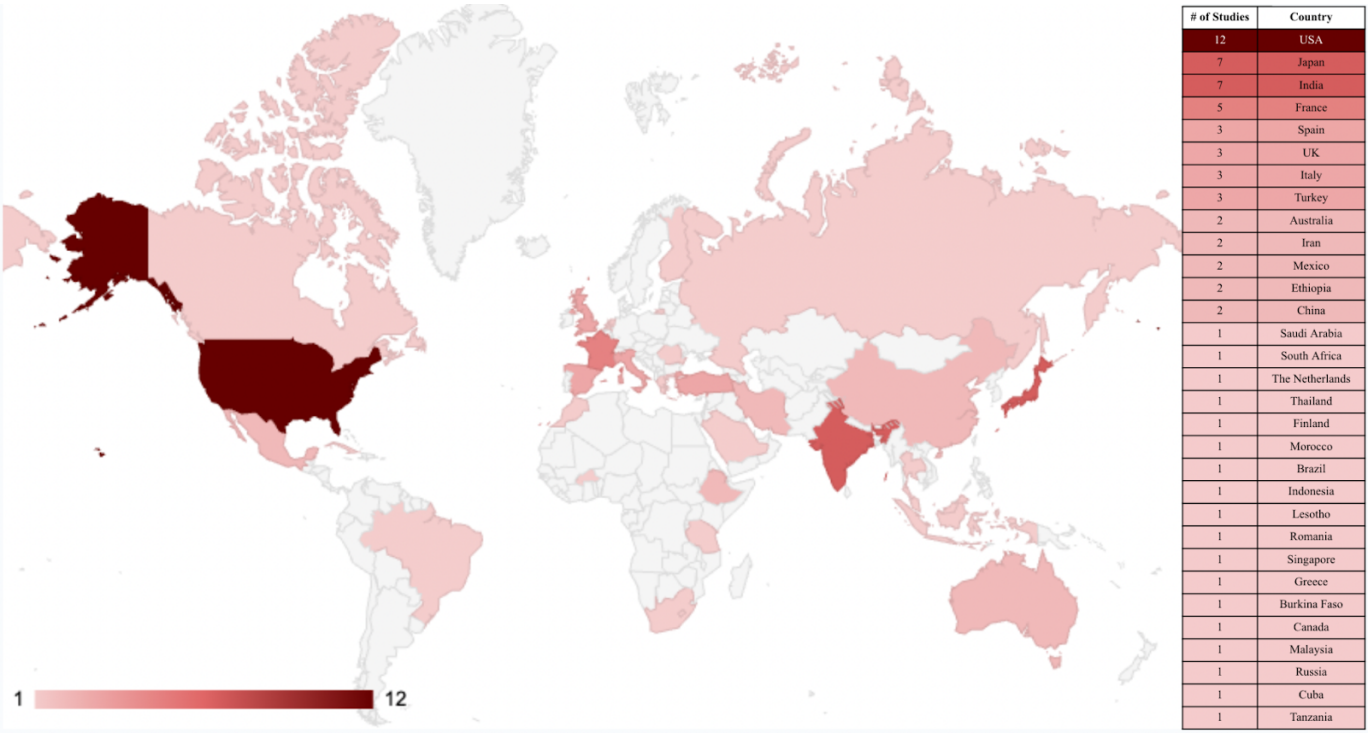
The Critical Appraisal assessment using the Joanna Briggs Institute Checklist for Case Reports resulted in 69 papers that met 8/8 of the criteria. One paper met 7/8 of the criteria, as it did not explicitly mention whether or not complications or adverse events occurred and how they might have been managed or if the patients survived event free. One other paper met 6 criteria and the other 2 were deemed 'not applicable' because while planned intervention was described, the patient died prior to surgery, and the postoperative course could not be discussed. In the end, all 71 papers were deemed eligible for the study.

Table 33: Critical Appraisal of Case Reports

Report ID	Income Level	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	?/8
1	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
2	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
3	High Income	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8
4	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
5	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
6	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
7	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
8	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
9	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
10	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
11	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
12	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
13	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	88
14	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
15	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
16	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
17	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
18	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
19	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
20	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
21	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
22	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
23	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
24	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
25	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
26	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
27	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
28	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
29	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
30	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
31	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
32	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
33	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
34	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
35	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
36	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
37	Low Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
38	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
39	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
40	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
41	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
42	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
43	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
44	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
45	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
46	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
47	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
48	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
49	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
50	Low Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
51	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
52	Low Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
53	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
54	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
55	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
56	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
57	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
58	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
59	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
60	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
61	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
62	Lower-Middle Income	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	6/6
63	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
64	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
65	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
66	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
67	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
68	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
69	Lower-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
70	High Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
71	Upper-Middle Income	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8

31 Countries were identified (Figure 26). Case Reports were sorted by the country in which patients received treatment, and these were stratified by income using World Bank classifications. 60.6% (n=43) of reports were from High Income Countries, 21.1% (n=15) were from Upper Middle Income Countries, 14.1% (n=10) were from Lower Middle Income Countries, and 4.2% (n=3) were from Low Income Countries (Figure 26).

Figure 26: Heatmap of the Number of Case Reports by Country



# of Studies	Country
12	USA
7	Japan
7	India
5	France
3	Spain
3	UK
3	Italy
3	Turkey
2	Australia
2	Iran
2	Mexico
2	Ethiopia
2	China
1	Saudi Arabia
1	South Africa
1	The Netherlands
1	Thailand
1	Finland
1	Morocco
1	Brazil
1	Indonesia
1	Lesotho
1	Romania
1	Singapore
1	Greece
1	Burkina Faso
1	Canada
1	Malaysia
1	Russia
1	Cuba
1	Tanzania

Figure 27: Percentage of Case Reports by Country Income Level

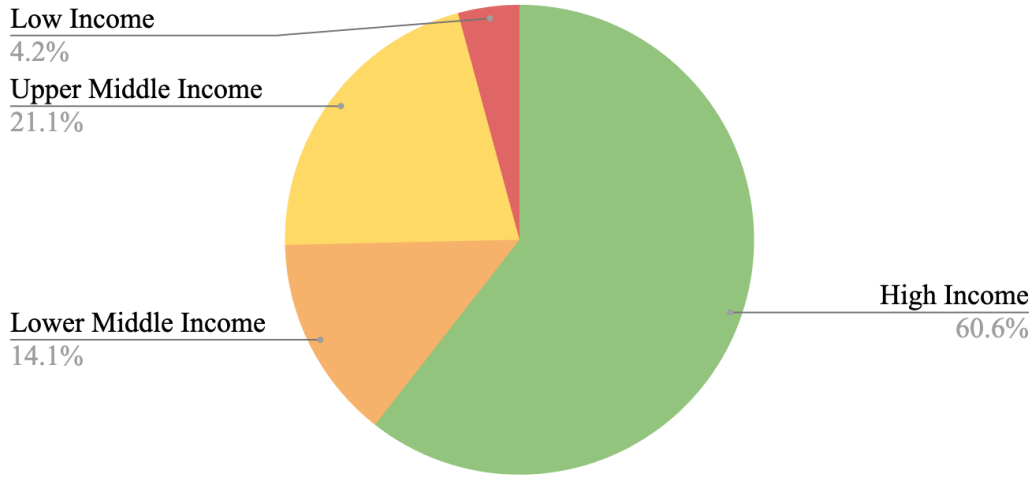
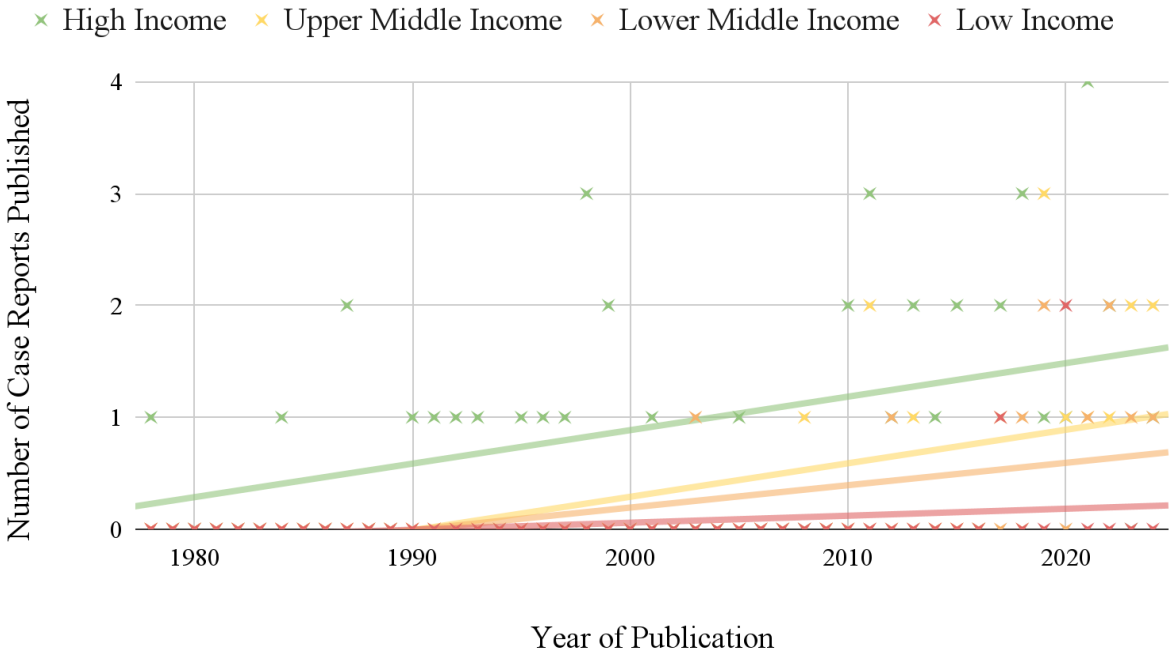


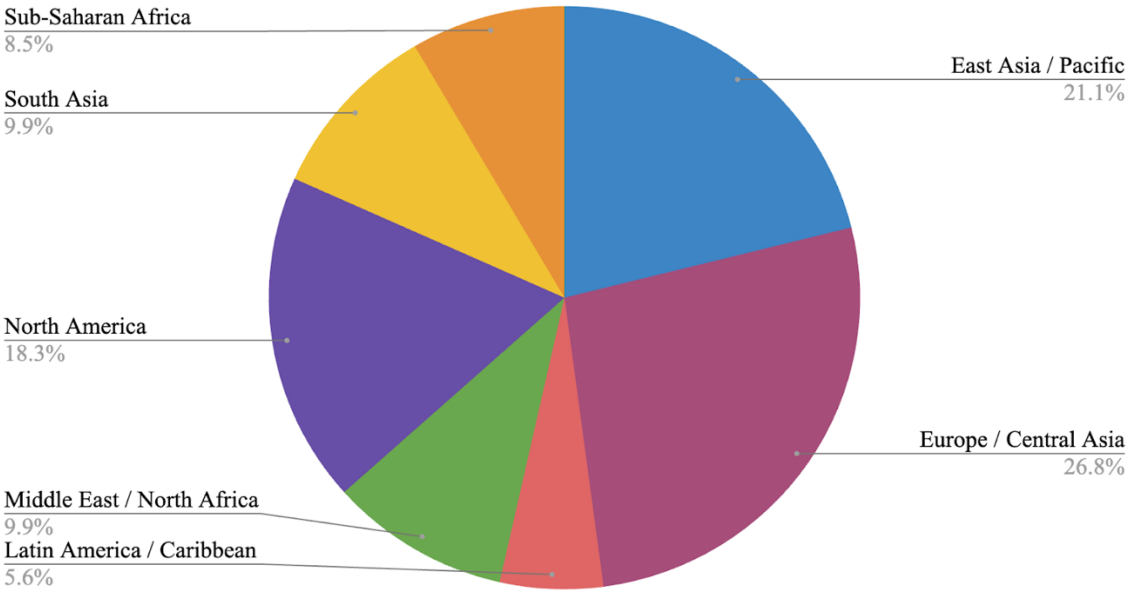
Figure 28 shows the frequency of Case Report publishing by country income level. High Income Countries consistently publish the most case reports averaging a slope (an increase) of m=0.0299 reports per year. Upper Middle Income Countries have the same average increase of reports published per year, while Lower Middle Income Countries have a slightly smaller slope at m=0.02 and Low Income Countries have the smallest slope of m=6.24E-03.

Figure 28: Case Reports by Country Income Level over the Years



Using World Bank classifications, we can also see a breakdown of case reports by region. The region that published the most reports (n=19) was Europe / Central Asia, followed by East Asia / Pacific (n=15) and North America (n=13). The Middle East / North Africa and South Asia published the same amount (n=7) followed by Sub-Saharan Africa (n=6). Latin America / Caribbean published the fewest Case Reports (n=4).

Figure 29: Percentage of Case Reports by Region



3.3.2 Patient Characteristics

From the 71 Case Reports, data was collected from 80 patients total with Neonatal Tumours. There were 30 males, 45 females, and 5 patients whose sex was unspecified, leaving a male to female ratio of 1 to 1.5.

The proportion of patients from High Income Countries was 61.3% (n=49), from Upper-Middle Income Countries was 18.7% (n=15), from Lower-Middle Income Countries was 15% (n=12), and from Low Income Countries was 5% (n=4).

40 types of tumours were identified in these studies, which were grouped into larger categories: Germ Cell Tumours (GCT) (n=44), Central Nervous System (CNS) Tumours (n=9), Soft Tissue Tumours (n=16), Renal Tumours (n=2), Blastomas (n=6), and Multiple (n=3) which accounted for patients presenting with more than one type of tumour at a time.

Figure 30: Breakdown of Patients by Tumour Category

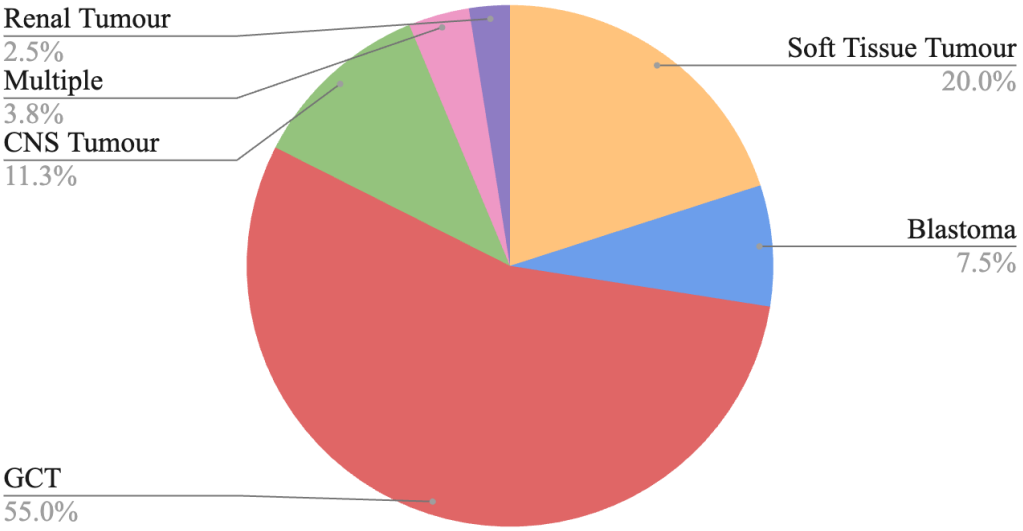


Table 34: Tumour Categories and Subcategories

Tumour Category	Tumour Subcategory	# of patients
GCT	Sacrococcygeal Teratoma (SCT)	16
	Oropharyngeal Teratoma	5
	Cervical Teratoma	5
	Thyroid Teratoma	2
	Retroperitoneal Teratoma	2
	Extracranial Teratoma	2
	Mediastinal Teratoma	2
	Mixed GCT	1
	Orbital Teratoma	1
	Facial Teratoma	1
	Yolk Sac Tumour (YST)	1
	Hepatic Teratoma	1
	Intranasal Teratoma	1

	Intrapericardial Teratoma	1
	Oral Teratoma	1
	Extranasal Teratoma	1
	Dermoid	1
	Pharyngeal Teratoma	1
CNS Tumour	Spinal Teratoma	2
	Teratoma of the CNS	2
	Glioma	1
	Astrocytoma	1
	Craniopharyngioma	1
	Medulloblastoma	1
	Cranial Haemangioma	1
	Hemangiopericytoma	1
Soft Tissue Tumour	Hamartoma	6
	Rhabdomyoma	2
	Rhabdomyosarcoma	2
	Lymphangioma	2
	Fibrosarcoma	1
	Fibroma	1
	Haemangioma	1
	Epulis	1
Renal Tumour	Mesoblastic Nephroma	2
Blastoma	Neuroblastoma	3
	Sialoblastoma	1
	Pleuropulmonary Blastoma	1

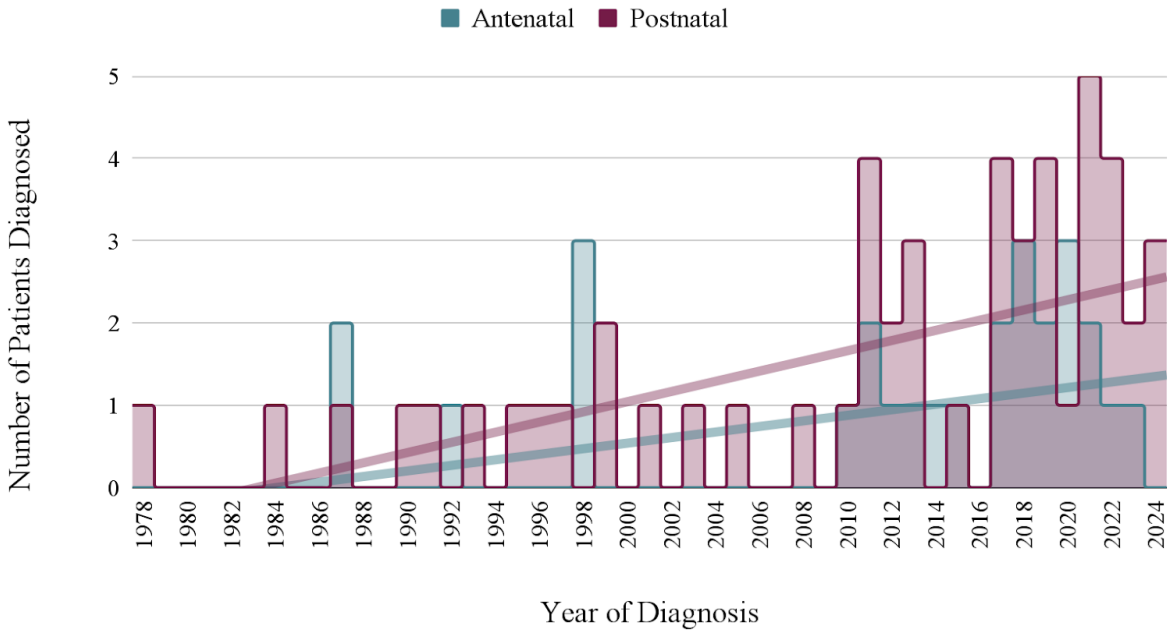
Multiple	Hepatoblastoma & Haemangioma	1
	Pancreoblastoma & Neuroblastoma	1

3.3.3 Observations

Within the Case Report population, 27 patients were diagnosed antenatally, 52 patients were diagnosed postnatally, and for 1 patient the time period of diagnosis was not reported. Excluding this last case, the ratio of antenatal to postnatal diagnosis is 1 to 1.9.

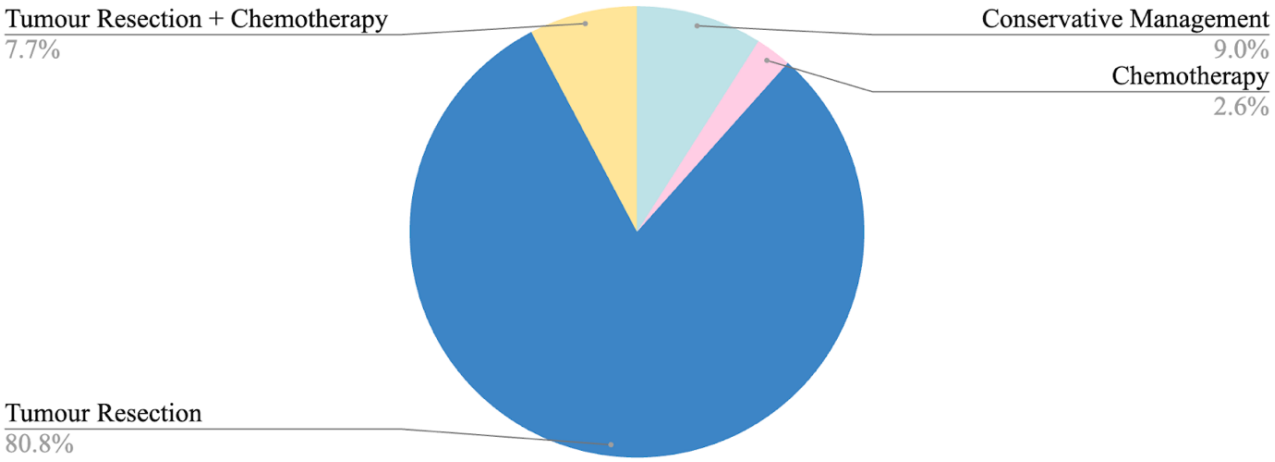
Figure 31 shows the proportion of cases reporting antenatal and postnatal diagnosis. Postnatal Diagnosis is consistently reported with more frequency averaging a slope (an increase) of m=0.0619 reports per year. Antenatal diagnosis has a smaller yet still positive slope (increase) of m=0.0338 reports per year.

Figure 31: Antenatal vs Postnatal Diagnosis over the Years



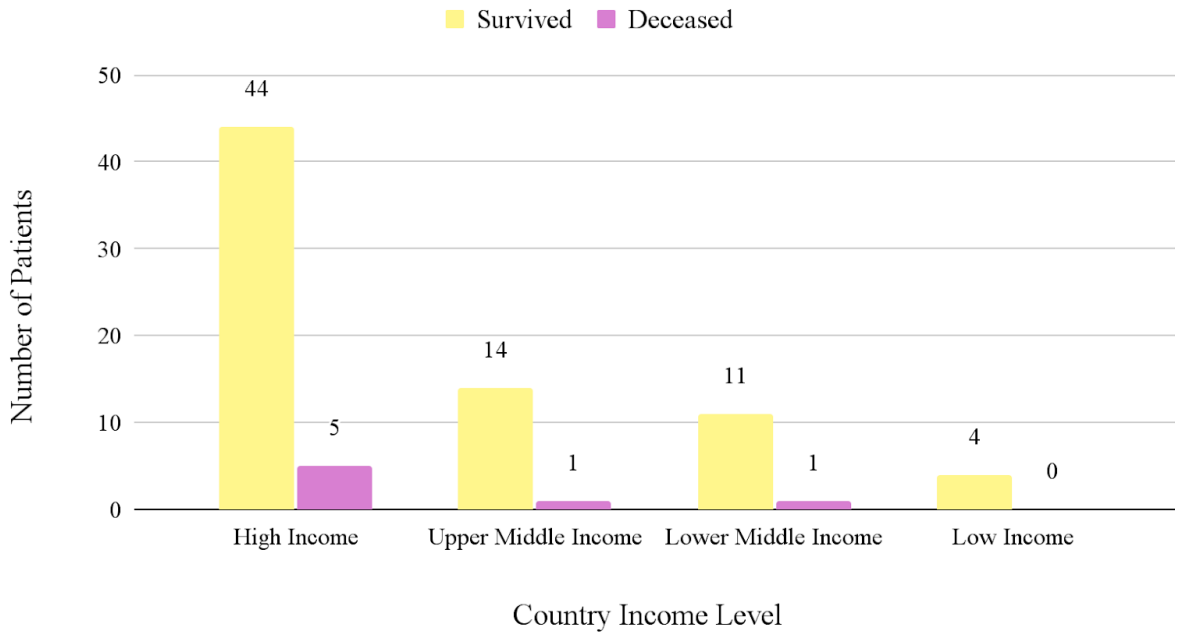
Within this population, 63 patients were treated with Tumour Resection surgery, 7 patients were treated with Conservative Management, 6 patients were treated with a combination of Tumour Resection and Chemotherapy, and 2 patients were treated with Chemotherapy on its own.

Figure 32: Breakdown of Patients by Intervention



Out of the 80 patients, 73 survived. There were 5 deaths and 44 surviving patients from High Income Country reports, 1 death and 14 surviving patients from Upper Middle Income Country reports, 1 death and 11 surviving patients from Lower Middle Income Country reports, and 0 death and 4 surviving patients from Low Income Country Reports.

Figure 33: Survival Reported in Case Reports by Country Income Level



Out of the 73 surviving patients, 63 survived Event Free. There were 8 patients with complications from High Income Country reports, 1 patient with a complication from Upper Middle Income Country reports, 0 patients with complications from Lower Middle Income Country reports, and 1 patient with a complication from Low Income Country reports.

Figure 34: Event Free Survival Reported in Case Reports by Country Income Level

By intervention, out of patients receiving Tumour Resection surgery 61 survived and 2 died, out of patients who were Conservatively Managed 6 survived and 1 died, out of patients receiving Tumour Resection and Chemotherapy 5 survived and 1 died, and out of the Chemotherapy patients 1 survived and 1 died. 2 patients were deceased before possible intervention.

Table 35: Case Report Patient Survival by Intervention

Intervention	Survived	Deceased	Total
Tumour Resection	61	2	63
Conservative Management	6	1	7
Tumour Resection + CT	5	1	6
Chemotherapy	1	1	2

3.3.4 Case Report Categorization

5 categories of Case Reports arose from the thematic analysis that was conducted: Management, Diagnostics, Unique Presentation, Rare Case, and Etiology / Pathogenesis. Table 36 details the final coding decisions, with thematic justifications for why each report meets the criteria to fit into a particular category.

Table 36: Categorization of Neonatal Tumour Case Reports

Management Diagnostics Unique Presentation Rare Case Etiology / Pathogenesis

ID and Title	Supporting Quote	Category and Themes
1. Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature	'We report a case of this association, review the world literature, and discuss prognosis and therapy.' 'The first reported case of concurrent presence of cutaneous and hepatic hemangiomata was by Bruchanow in 1899.1 No treatment was given and the patient succumbed at four months of age. There have been 57 subsequent cases reported in the world literature. The complete triad of cutaneous hemangiomata, hepatic hemangiomata, and congestive heart failure was present in 69% of the cases.'	Unique Presentation • Uncommon feature (association / comorbidity)
2. Cervical neuroblastoma in a newborn infant	'A case of cervical neuroblastoma is presented. It was treated by surgical resection followed by homolateral node dissection. No chemotherapy or radiotherapy was done, and patient is free of disease at the present time.' 'We comment on the low incidence of this tumour in newborn and in cervical location, and on the good response of these forms to surgical treatment only.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment
3. Cystic sacrococcygeal teratoma: ultrasound diagnosis and perinatal management	'Our cases add further support to the contention that presentation in the latter weeks of gestation is associated with a better prognosis. The favorable outcome, ever, is more likely due to the triad of prenatal detection, planned intrapartum management, and prompt surgical resection. Case 1 illustrates the benefits of prenatal diagnosis in planning intrapartum management. In this case, although the tumor was cystic and 21 cm in size, caesarean section delivery was accomplished without decompression or rupture of the tumor. In Case 2, the prenatal detection of a rare intra abdominal cystic SCT	Diagnostics • Advocating [early] detection (prenatal screening). • Failures or successes in diagnosis

	prevented a delay in management, thereby minimizing the potential risks of malignant degeneration, and urinary tract obstruction.'	
4. Juvenile digital fibroma: apropos of 2 cases	'The authors report 2 cases of infantile digital fibromatosis. These benign tumours occur in newborns and infants, involving mainly the extremities (fingers, toes).' 'The diagnosis of such fibrous tumours is useful since surgical treatment can be avoided in a majority of cases.' 'Treatment of FDJ can be divided into dermatological and surgical treatments (all treatments taking into account the benign nature of the lesion). Abstention from treatment seems legitimate in the absence of functional repercussions.' 'Radiotherapy has been abandoned as ineffective and dangerous.'	Management • Advocating the use of a technique or treatment • Recommend standardization of perioperative practices
5. Progressive tumor necrosis and lethal hyperkalemia in a neonate with sacrococcygeal teratoma (SCT)	'Clinically significant hyperkalemia is very rare in neonates and infants who have normal renal function.' 'Hyperkalemia associated with tumor lysis can be seen occasionally in children and adults at the initiation of chemotherapy for lymphocytic malignancies.' 'Solid tumors, in general, are not known to undergo spontaneous lysis.' 'Reviewing 541 cases of SCT that were published through the years in the Journal of Pediatric Surgery, there were 31 (5.7%) operative or immediate postoperative deaths. Of these 31, 4 were documented as having cardiac arrest, and 8 were classified as 'unknown cause.' It is quite possible that among the latter eight, some may in fact have had undetected hyperkalemia that caused cardiac malfunction and death. Because hyperkalemia was not recognized until now as a significant factor in the outcome of babies with SCT, we suggest that frequent determinations of serum K along with acid-base status be undertaken preoperatively, especially in those neonates manifesting tumor lysis.'	Unique Presentation • Uncommon feature (symptom)
6. Giant supratentorial meningeal haemangiopericytoma in a newborn	'We report a case of a huge right hemispheric tumour operated upon successfully in a child 5 days old, who had a total tumoural excision and an uneventful outcome with 5 months follow up. This tumour appears to be the first meningeal haemangiopericytoma described in a newborn. Adequate treatment and histological findings are discussed.'	Rare Case • First documented case of meningeal haemangiopericytoma in a neonate • Landmark paper

	'No meningeal hemangiopericytoma in a newborn as far as we know has been described.'	
7. New approach to the management of airway obstruction in 'high risk' neonates	'To our knowledge, this is the first extrauterine surgical procedure successfully performed using this technique. A new approach to airway management in 'high risk' neonates involving the cooperative efforts of pediatricians, neonatologists, anesthesiologists, and otolaryngologists is presented'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment
8. Neonatal medulloblastoma	'Neonatal brain tumors are rare, and there have been only 24 cases of neonatal medulloblastoma. The prognosis for these patients is extremely poor, regardless of treatment. Surgery, radiation and chemotherapy for neonatal medulloblastoma are discussed.' 'The results of treatment of neonatal medulloblastoma are disappointing, and the numerous problems encountered, such as the difficulty of the surgical procedure and adverse effect of radiation therapy remain unsolved.' 'We describe our efforts to treat this patient, which included surgery, radiotherapy and chemotherapy and discuss the relevant literature.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices • Treatment of a unusual case
9. A huge immature cervical teratoma in a newborn: report of a case	'The management of a pediatric cervical teratoma should also be similar to that of a sacrococcygeal teratoma.' 'Case of a neonate with a cervical teratoma is herein presented, along with a description of the radiological diagnosis and preoperative planning.' 'For infants or adults a therapeutic strategy similar to that for sacrococcygeal malignant teratomas 22'23 is recommended for malignant cervical teratomas, because in such patients the prognosis is reported to be relatively poor.'	Management • Recommend standardization of perioperative practices • Failures or successes in treatment
10. Hairy polyp of the oropharynx: case report and literature review	'Hairy polyp of the oronasopharynx is an uncommon developmental malformation that is most frequently seen as a pedunculated tumor in the neonate.' 'The clinical presentation of the infant with HP is dependent on the size, shape, and location of the lesion. Signs and symptoms may include feeding difficulties, vomiting, intermittent mild respiratory difficulties, asphyxia, hemoptysis, unilateral Eustachian tube dysfunction, unilateral nostril drainage, and a detectable mass.' 'HPs are uncommon developmental malformations that occur in infants and children.'	Unique Presentation • Uncommon feature (presentation / symptoms)

11. Hydrops fetalis and fibrosarcoma: case report of an uncommon association	'Fetal hydrops associated with neonatal tumours is an uncommon occurrence.' 'Another peculiarity of neonatal tumours is their clinical presentation as hydrops fetalis. The association of congenital tumours with hydrops fetalis has been described with neuroblastomas, teratomas and haemangiomas but, to our knowledge, this is the first occurrence of hydrops fetalis and fibrosarcoma' 'We conclude that the association of hydrops fetalis and fibrosarcoma is an exceptional observation but can be added to the long list of differential diagnoses of non-immune hydrops.'	Unique Presentation • Uncommon feature (association / symptom)
12. Cervical teratoma: prenatal diagnosis and long-term follow-up	'Prenatal diagnosis allows for early consultation with paediatric surgical specialists, so that the time and place of delivery can be addressed, and planning for resuscitative efforts can be organized in advance. If the airway is quickly stabilized and resection of the tumour is not delayed, the prognosis is good.' 'We present a review of the literature, with attention to outcome and potential for malignancy in neonatal cervical teratomas, in order to provide help in decision-making, once prenatal diagnosis is made.'	Diagnostics • Advocating [early] detection (prenatal diagnosis).
13. Laparoscopic clipping of the median sacral artery in huge sacrococcygeal teratomas	'Huge sacrococcygeal teratomas in the newborn can cause significant morbidity and even death due to cardiac failure, hemorrhage, or both. Surgical removal is the treatment of choice, but can indicate these events. Ligation of the median sacral artery, which always supplies the tumor, prior to its removal has been advocated, but in the past this procedure required a formal laparotomy. Nowadays, it can be easily accomplished laparoscopically, as this case report demonstrates.'	Management • Advocating the use of a technique or treatment • Recommend standardization of perioperative practices
14. Perinatal and perianesthetic management of the sacrococcygeal teratoma in a neonate	'We report perinatal and perianesthetic management of a female infant with sacrococcygeal teratoma who underwent fetal bladder puncture and postnatal tumor resection.' 'It is important for good patient outcomes to evaluate preoperatively the risks mentioned above'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices

15. Anesthetic management for newborn pharyngeal teratoma. [Japanese]	'We report anesthetic management of a newborn with epignathus who underwent tumor resection. He was delivered vaginally at 39 weeks of gestation and Apgar scores were 9 at 1 and 5 min.' 'Tumor was resected with blood loss of 103 gm. The trachea was extubated on the third postoperative day and the postoperative course was uneventful. For safe management of cases of pharyngeal teratoma, careful preoperative assessment of the airway is most important and sufficient preparation and careful intubation are mandatory to keep airway patent. The perioperative bleeding from the tumor and the airway obstruction by the tumor or its remnant after the excision could also be hazardous to the airway.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices
16. Epignathus: a germ-cell tumour presenting as neonatal respiratory distress	'The only way to preempt acute upper airway obstruction after birth in these patients is to diagnose the nasopharyngeal teratomas antenatally' 'Once antenatal diagnosis of the tumour is made appropriate measures can be taken at the time of delivery, including the presence of a paediatrician, a paediatric otolaryngologist and a paediatric intensivist.' 'The important point to make is that many neonates with nasopharyngeal teratomas are diagnosed after birth, and under these circumstances it falls to the attending clinicians to save the child's life by acting quickly and efficiently.'	Diagnostics • Advocating early detection (prenatal screening) • Emphasizing or presenting diagnostic markers
17. Life-threatening mediastinal teratoma in a neonate	'This report describes a newborn with a large mediastinal teratoma (MT) presenting with severe respiratory distress (RD) at birth. At operation, there was no space for dissection because the huge cystic and solid tumor completely occupied the left hemithorax. After evacuation of the cystic component, the tumor was removed successfully. To our knowledge, only 16 newborn infants with MT presenting with RD have been reported. Operative morbidities occurred in one-half of the cases. We have reviewed the literature to discuss the potential risks of this entity.' 'Usually, neonatal MTs presenting with respiratory symptoms are so large that they occupy nearly the whole hemithorax. Therefore, if the tumor has cystic components, aspiration of the cysts is indicated to reduce the tumor volume and secure an operative field. In our experience evacuation of the cyst was very effective in manipulating the tumor.'	Management • Failures or successes in treatment • Treatment of an unusual case

18. Extranasal glial heterotopia: case report	'Glial heterotopia or the occurrence of isolated non-teratomatous extracranial glial tissue is rare. We report a neonate with extensive extranasal glial heterotopia involving the left buccopharyngeal region, palate and base of the skull and presenting with respiratory distress and a bleeding oral mass.' 'The occurrence of isolated extracranial glial tissue is rare, and the majority of these are located in the head and neck.' 'Extranasal sites of glial heterotopia are rarer. We report a rare case of a neonate with extensive extranasal glial heterotopia.'	Unique Presentation • Uncommon feature (location and symptoms)
19. Multiple congenital cranial hemangiomas	'Though cranial hemangiomas are second only to vertebral hemangiomas in frequency, such lesions are rarely congenital and multiple. It is probable that the true incidence of congenital calvarial hemangiomas is higher than that reported in the literature, as they are unlikely to undergo imaging, most being asymptomatic and without a significant soft tissue component. We present a case of multiple congenital calvarial and skull base cavernous type hemangiomas, diagnosed in a 4-day-old female, involving the right zygoma, maxilla, frontal and petrous temporal bones and contralateral squamous temporal bone.' 'Despite being the most common soft tissue tumor of infancy and childhood, the osseous form of hemangioma is rarely described in children. Congenital lesions are even rarer. To the best of our knowledge, this is the first reported case of multiple congenital osseous hemangiomas involving the calvarium.'	Rare Case • First Case of (multiple calvarial and skull base cavernous type hemangiomas) in (neonates)
20. Multiple congenital oral granular cell tumours in a newborn black female: a case report	'Congenital oral granular cell tumour of the newborn is an uncommon benign tumour of uncertain origin.' 'The occurrence of congenital epulis in non-Caucasians is rare.' 'to our knowledge this is the first case to be reported in a black South African infant.' 'CGCT is uncommon and occurs almost exclusively in Caucasian newborns.' 'CGCT is relatively common in Caucasian newborns but appears to be much less common in black newborns, and the occurrence of more than one lesion in a black infant is rare.'	Rare Case • First Case of (multiple oral granular cell tumours) in (Black neonate in South Africa)

21. Perinatal evolution of mesenchymal hamartoma of the chest wall	'We present serial measurements of an antenatally detected MHCW (8 antenatal ultrasounds and 2 postnatal computed tomographic scans). The study demonstrates that the relative tumor size peaked at birth and then decreased postnatally. Based on this evidence, we believe that MHCW can be managed conservatively in an asymptomatic patient.' 'The results consistently suggest a reduction of tumor volume postnatally. Conservative treatment in our asymptomatic patient is supported by this piece of evidence.' 'Conservative management of asymptomatic children with MHCW is feasible in centers with contemporary diagnostic imaging, the capacity to regularly monitor the patient, and the availability of surgical intervention when necessary.'	Management • Advocating the use of a technique or treatment • Recommend standardization of perioperative practices
22. Simultaneous occurrence of pancreatoblastoma and neuroblastoma in a newborn with beckwith-wiedemann syndrome	'PB or infantile pancreatic carcinoma is a rare pancreatic tumor; not more than 70 cases have been reported in the literature and almost all of them have been in childhood. Only 6 cases associated with BWS have been described, all of which occurred in the neonatal period. We report a case of a newborn with BWS presenting the simultaneous occurrence of a cystic PB and an adrenal NB; to our knowledge no other similar cases have been described in the literature.' 'Only 6 cases presenting the association of BWS and PB have been described in the literature, and our case is the first in which there is a concomitant occurrence of BWS, PB, and NB.' 'In conclusion, patients with BWS may have various types of concomitant tumors and our report is the first in the literature to describe the association of PB and NB in a Newborn.'	Rare Case • First Case of (Pancreatoblastoma and Neuroblastoma) in (Newborn (with beckwith-wiedemann syndrome)) • BWS - might be uncommon association - but also first of PB and NB
23. Intrapericardial teratoma in neonates: a surgical emergency	'The authors report a rare case of a neonate who presented with respiratory and cardiac compromise due to cardiac tamponade necessitating emergency exploration of the pericardium and excision of tumor.' 'Intrapericardial teratoma in neonates is a surgical emergency if presented with significant pericardial effusion. It can be a challenge if diagnosed in utero with rupture before the viability of pregnancy. A multidisciplinary team approach is necessary to manage such situations. Complete excision is necessary because of its association with tissues of malignant potential.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Treatment of an unusual case

24. Management and treatment of a sialoblastoma of the submandibular gland in a neonate	'We report one case of sialoblastoma of the submandibular gland; we describe its clinical, radiological and histopathologic features and discuss the differential diagnosis and treatment.' 'Objectives: Report a rare congenital salivary gland tumor and its clinical, radiological and histopathologic aspects. Discuss differential diagnosis and treatment.' 'When they are completely resectable, surgical resection is the mainstay for treatment of these tumors and no adjuvant therapy is needed.' 'There is no uniform approach to management of sialoblastoma in the literature. Early surgical therapy is the mainstay for the treatment of these tumors and complete excision with negative margins seems to be curative. However, as recurrences have been reported as late as 4 years after excision, the follow up has to be frequent and prolonged'	Management • Treatment of an unusual case • Recommend standardization of perioperative practices
25. Mediastinal teratoma in a neonate with acute respiratory failure	'Neonates with large mediastinal teratomas generally show severe respiratory distress, and immediate surgical treatment is needed to alleviate their problems.' *'Objectives:* Report clinical symptoms, diagnostic procedures, treatment option, and outcomes after the treatment for a neonate with a large mediastinal teratoma.' 'The successful management of a neonate with large mediastinal teratomas was presented. Immediate detection and proper treatment of the large mediastinal teratoma in a neonate was most important to decrease the morbidity and mortality of the infant.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment
26. Peripartum ultrasound-guided drainage of cystic fetal sacrococcygeal teratoma for the prevention of the labor dystocia: a report of two cases	'The authors report in details two SCT cases with uncomplicated vaginal delivery after peripartum ultrasound-guided drainage of the cystic teratoma. We conclude that the percutaneous emptying of the cystic SCT is an easy, encouraging, safe, and efficient procedure and enables normal vaginal delivery, thus avoiding labor dystocia and possible complications of the cesarean delivery and the risk of tumor rupture.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Recommend standardization of perioperative practices

27. Surgical treatment of huge congenital extracranial immature teratoma: a case report	'Neonatal teratomas are rarely located in the scalp. In the literature, there were only a few patients who underwent surgery during the neonatal period with a good outcome; however, all such patients survived. In this paper, we present a neonatal case of huge congenital extracranial immature teratoma on the scalp extending to the orbita, ears, and brain.' 'A total surgical excision was performed and histopathological examination showed immature teratoma. The patient's early postoperative course was uneventful.' 'We conclude that acceptable functional outcomes in the context of massive congenital craniofacial teratomas can be achieved by early radical resection.' 'The best care of these children is offered through a combined neurosurgical and craniofacial approach.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Recommend standardization of perioperative practices • Treatment of an unusual case
28. Cervical teratoma: report of 2 cases. [French]	'Cervical localization is rare and requires multidisciplinary management. Prenatal diagnosis is essential given the risk of respiratory distress. It is still rarely performed in our context, and therefore delays treatment.' 'Treatment is surgical. Prenatal diagnosis allows for better management of these patients due to the risk of respiratory distress at birth due to compression. The prognosis depends primarily on respiratory signs and whether or not the condition is malignant.'	Diagnostics • Advocating [early] detection (prenatal screening) • Emphasizing or presenting diagnostic markers
29. Teratoma showing the features of retinal structure: A case of sacrococcygeal teratoma	'This observation shows that polarized structures, including the normal retina and retina-like structure, need a gradient of concentration of oxygen or blood flow during formation and structural development, especially under hypoxic conditions' 'In conclusion, we have reported a case of sacrococcygeal teratoma with a retina-like structure in a newborn and suggested the importance of blood supply and oxygen circumstance in the formation of the stratified structure.'	Etiology / Pathogenesis • Considering the how a specific phenotype/subset of the disease arises
30. Congenital giant craniopharyngioma	'Craniopharyngioma is a rare neonatal tumor with only eight cases reported. The management of this tumor in the neonatal period is still controversial, with the best results obtained when radical resection is performed. We present the case of a patient who received the diagnosis of a suprasellar tumor during the prenatal period and reviewed literature regarding the management.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment

	‘The present case is the ninth diagnosed during the prenatal period and the literature is controversial on the management of this rare tumor. The complete excision of the lesion using the microsurgical technique is the gold standard treatment for these patients; however, there are many factors that limit this approach in neonates.’ ‘We present the case of a patient who received the diagnosis of a suprasellar tumor during the prenatal period and underwent neurosurgical treatment.’ ‘On the 14th day of life, the patient underwent a parietal craniotomy using the transcortical transventricular approach, planning the radical resection of the tumor, obtaining biopsy material for diagnosis, and treating the obstructive hydrocephalus’	• Recommend standardization of perioperative practices • Treatment of an unusual case
31. Epignathus teratoma: diagnostic and neonatal management; a case report	‘When it is undiagnosed prenatally, mortality is close to 100 % at birth, because of obstruction of the upper airways. We present a case of epignathus teratoma detected during obstetrical ultrasound screening. Diagnosis enabled planning for a safe delivery in a suitable multidisciplinary unit and use of the EXIT procedure.’	Diagnostics • Advocating [early] detection (prenatal screening) • Failures or successes in diagnosis
32. Management of symptomatic mesenchymal hamartoma of the chest wall: surgical resection only in symptomatic cases	‘Traditionally, the treatment of choice was an ‘en bloc’ resection, but surgery limited to symptomatic cases is now suggested by most authors due to the numerous cases of spontaneous regressions. We report 2 patients of symptomatic MHCW, characterized by progressive respiratory distress, who underwent surgical treatment with prompt resolution of symptoms.’ ‘After a proven pathological diagnosis of MHCW is obtained, surgical resection should be limited only to symptomatic patients.’	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Recommend standardization of perioperative practices
33. An infant with pleuropulmonary blastoma type II detected during the prenatal period	‘Only three cases of PPB diagnosed during the prenatal period have been reported in the previous literature, all of which involved PPB type I. We herein report the case of a female infant with PPB type II detected on maternal ultrasonography. The patient underwent surgical resection with adjuvant postoperative chemotherapy in the neonatal period due to persistent respiratory instability. According to the previous literature, the prognosis of type II and III disease is less favorable than that of type I. The present patient	Rare Case • First Case of (PPB type II) in (prenatal period) • Landmark

	achieved 11 years of disease-free-survival. To our best knowledge, this is the first report of PPB type II diagnosed during the prenatal period.' 'In conclusion, we herein reported a rare case of PPB type II detected in the prenatal period. The possibility of PPB should be taken into consideration in the differential diagnosis of pediatric pulmonary disorders including cystic lung diseases.'	
34. Combined endonasal and neurosurgical resection of a congenital teratoma with pharyngeal, intracranial and orbital extension: Case report, surgical technique and review of the literature	'This study reports a patient with a large teratoma involving the oropharynx, the nasopharynx and the left orbit, with intracranial extension. This case represents one of the first reported instances of such an association.' 'This type of teratoma is very rare and surgical morbidity is common' 'A review of the literature reported only 30 congenital head and neck teratoma cases with intracranial and extracranial extensions. Of these 30 cases, 6 were stillborn, 7 died in the first year, 15 were living at the time of publication, and 2 have an unknown status.' 'Head and neck teratomas with intracranial extensions are exceedingly rare.'	Unique Presentation • Uncommon features (associations / extensions)
35. Early intrauterine development of mixed giant intracranial teratoma in newborn: a case report	'We present a 34 weeks premature infant, born by C-section with a giant intracranial tumor' 'Neurosurgical examination concluded that the case is outside the therapeutic possibilities, with no chances of survival.' 'After 25 days of thermal comfort... a fatal severe episode of apnea occurred.' 'A giant teratoma with poor vital prognosis and fatal outcome represents a high challenge for clinicians, as prolonged sufferance is frustrating for both parents and professionals. Ethical aspects are to be considered, similar to the situation of anencephalic cases that survives several days, even weeks, despite providing only basic care.' 'G3 type complex teratoma, even if rare, can be localized at the cerebral level and get huge development and growth only in the third trimester of pregnancy, ending with a neonate that has no chance of survival. Such cases cannot benefit of therapeutic interruption of pregnancy and generates serious difficulties for parents and clinicians. Early intrauterine detection by ultrasound and, if necessary, even MRI, could prevent the birth of such newborns and their survival with no quality of temporary life. More research to identify a significant marker to detect the development of such tumor is necessary.'	Diagnostics • Advocating early detection (prenatal screening → termination of pregnancy) • Failures or successes in diagnosis • Emphasizing or presenting diagnostic markers

36. Anaesthesia management of a newborn with giant sacrococcygeal teratoma. [Turkish]	'During excision of this teratoma in neonates, hemorrhage can be associated with serious perinatal morbidity and mortality. In this case report, we present anaesthesia management of 4450 g male newborn on postnatal 3rd day who was born by caserean delivery with 15x10 cm sacrococcygeal teratoma at gestation of 38 weeks. In this report, the importance of preoperative meticulous preparation and intraoperative close hemodynamic monitorization are emphasized.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices
37. Case report: A rare presentation of spinal teratoma in neonates: Two cases from Ethiopia	'Teratomas are tumors with foreign tissues with a different biological behavior from the anatomic locations. The sacrococcygeal region is one of the favorite sites for extra gonadal teratomas, which is also the commonest site for spinal teratomas' 'Occurrence of teratomas at the lumbar area is a rare anatomical anomaly and its association with dysraphysm is rarely described. Here we report 2 cases; the first skin covered and the second multicystic lumbar mass with dural extension and spinal dysraphysm. Both have other associated anomalies. Both patients had satisfactory surgical outcomes.'	Unique Presentation • Uncommon features (locations and associations)
38. Management of mixed type congenital mesoblastic nephroma: Case series and review of the literature	'Congenital mesoblastic nephroma (CMN) is the most common renal tumor of infancy; however, it occurs infrequently with an incidence of 1 : 125,000. The cellular and classical variants are the most common subtypes of tumors, with a mixed variant occurring infrequently. We describe two cases of mixed variant CMN' 'CMNs are currently classified into one of three distinct categories. These categories play a major role in determining therapy and prognosis. The most common type of CMN, accounting for 66% of cases, is the cellular type… The classic type, which occurs less frequently making up 24% of cases of CMN… A third, much less common type of CMN, can also occur. This is the mixed type, which has components of both classical and cellular and occurs in only 10% of cases. The degree of relapse for this type of tumor is not well described. Both of our patients were ultimately diagnosed with this rare type of tumor.' 'Prompt recognition and treatment is important for optimal outcomes for these infants.'	Unique Presentation • Uncommon features (variant/ subtype)

39. Massive facial teratoma managed with the ex utero intrapartum treatment (EXIT) procedure and use of a 3-dimensional printed model for planning of staged debulking	'We present a case of an antenatally diagnosed massive facial teratoma originating from the pterygomaxillary fossa, which was associated with polyhydramnios and preterm birth. We managed this complex tumor with an ex utero intrapartum treatment (EXIT) procedure, multidisciplinary medical and surgical team, and staged excision and reconstruction aided by use of a 3-dimensional printed model. Here we review the surgical management of this rare and complex tumor.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Treatment of an unusual case
40. Congenital Rhabdomyosarcoma: a different clinical presentation in two cases	'RMS can also be diagnosed during the neonatal period. Given the young age, disease management is often challenging, and especially for the alveolar subtype, the outcome is dismal despite intensified multimodality therapy. In fact, it characteristically manifests with multiple subcutaneous nodules and progression most commonly occurs in the CNS.' 'In this context, CNS prophylaxis could play a role in preventing leptomeningeal dissemination, and molecular studies can allow a deeper tumor characterization, treatment stratification and identification of new potential therapeutic targets.' 'We report the clinical, radiological and histological characteristics of these patients, as well as therapeutic approach and outcome, together with a literature review of congenital RMS.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment
41. Diagnosis and prenatal prognosis of fetal lymphangioma. Two cases reports. [Spanish]	'Two uncommon clinical cases, due to their location and extension, of fetal lymphangiomas are reported. In both patients, the diagnosis was established by ultrasound study, during the third trimester, in low risk gestations.' 'Ultrasound is a decisive test for the detection and diagnosis of fetal lymphangiomas. Genetic testing and counseling are essential for pregnant patients with suspected cases of these disorders.'	Diagnostics • Advocating early detection (ultrasound and genetic testing). • Failures or successes in diagnosis • Clarifying differential diagnosis
42. Diagnosis and Surgical Management of Congenital Intranasal Teratoma in a Newborn: A Rare Case Report	'In this report, we describe a case of a mature teratoma arising from the roof of the nasal cavity presenting as an isolated intranasal mass, the first of its kind from our literature review. The tumor was resected endoscopically with no recurrence detected.'	Rare Case • First Case of (Intranasal Teratoma) in (newborn) • Landmark

	'In summary, we report the first case of a congenital teratoma arising from the roof of the nasal cavity that has been successfully resected via an endoscopic approach.'	
43. Teratoma Arising from Hepato Duodenal Ligament in the Newborn with Transection of Portal Vein, Hepatic Artery and Common Bile Duct: A Surgical Challenge	'A 7-day-old neonate presented with a large intra-abdominal mass adherent to the hilum of the liver encasing the portal triad… survival in neonate following total transection of portal triad is rare and has not been reported.' 'It is extremely rare to present in the hilum of the liver extending on to the hepatoduodenal ligament. Surgery carries risk of injury to vital structures in porta hepatis.' 'In this child, the tumor was arising in the region of the hilum of the liver extending on to the capsule of the left lobe of the liver from which it could not be separated. Teratoma arising from hepatoduodenal ligament producing portal hypertension has been described. Twenty-seven children with giant liver tumors involving the hepatic hilum have been described with one teratoma and the rest being malignant tumors. However, these are primarily liver tumors extending on to hilum of liver. In this child, histologically, the liver parenchyma was not seen in the tumor.' 'The case is presented for its rarity in the location of teratoma and survival following repair of total transection of the portal vein, hepatic artery, and common bile duct. Such case in a neonate has not been reported so far.'	Unique Presentation • Uncommon features (location, structure, survival)
44. Cervical Giant Immature Teratoma in a Newborn: A Challenge for Survival	'Complete excision of the tumour prevents malignant transformation. Timing of the surgery is based on severity of airway compromise. Surgical outcome and survival depend on pre-existing pressure effects, operative injuries to the vital structures and also co-existing comorbidities. One such complicated case of giant cervical teratoma is described here.' 'In antenatally diagnosed cases, airway is secured either by *ex utero* intrapartum treatment procedure or by extracorporeal membrane oxygenation. If airway is not secured, an aggressive surgical exploration has to be done by a team with adequate expertise.' 'Giant cervical immature teratoma with PAH in a surviving neonate as reported here is of interest because of its rarity and survival is possible with aggressive multidisciplinary approach.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices • Treatment of an unusual case

45. Giant sacrococcygeal teratoma in newborn: A rare case	'Ultrasonography (USG) is a reliable diagnosis of work-ups during the prenatal period, followed by CT Scan after born. It is also required to decide management after delivery. Most SCT are benign and produce better outcomes if early surgical intervention is initiated soon after born.' 'Antenatal diagnosis is very crucial to prevent fetal and neonatal death. Imaging technology using ultrasound and CT Scan allows the prenatal and postnatal diagnosis of SCT. Surgical resection remains primary management to save life.' 'Antenatal USG was repeated for about 10 times until the day of delivery and shows a progressive growth of the tumor and polyhydramnios.' 'Regular antenatal check-ups and ultrasonography are recommended for all pregnant mothers to avoid organ dysfunction, diminished quality of life, and mortality. Early diagnosis and proper surgical intervention have the best outcome in most cases.'	Diagnostics • Advocating early detection (USG, CT). • Failures or successes in diagnosis • Emphasizing or presenting diagnostic markers
46. Mature sacrococcygeal teratoma: A case report	'A three day old female baby presented with a mature sacrococcygeal teratoma containing well-developed limb buds. She had surgical excision and primary repair with good results. A two-year follow up utilising serial serum alpha-fetoprotein assay and CT Scan revealed no evidence of tumour recurrence.' 'Complete excision is the primary therapy and is adequate if the tumour is benign. Chemotherapy and radiotherapy are however indicated in malignant cases and in recurrence after previous excision.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices
47. Mesenchymal hamartoma of the chest wall in a newborn: A case report study	'The findings of this case report yielded that mesenchymal hamartoma is a benign lesion presenting with aggressive clinical, radiological, and histopathological characteristics that can be mistaken for malignancy.' 'Since imaging studies are helpful for the diagnosis of mesenchymal hamartoma and CT scan generally is able to demonstrate intralesional and multifocal calcification, we used this technique for the diagnosis.' 'Mesenchymal hamartoma may be misdiagnosed with enchondroma, fibrous hamartoma, malignant mesenchymoma, and aneurysmal bone cyst. We can achieve definitive diagnosis only by resorting to histopathological examinations.' 'We came to this finding that mesenchymal hamartoma usually has a benign course, although it may have aggressive radiological and histological features.'	Diagnostics • Advocating detection (imaging, CT, histopathological exams). • Failures or successes in diagnosis • Avoiding misdiagnosis

48. Prenatal diagnosis of a sacrococcygeal teratoma: Case report	'The case is presented of a sacrococcygeal teratoma found in the prenatal diagnosis. It was observed in the sacral region as a rounded image with regular, defined, heterogeneous borders of 8.8 6.9 8.4 cm, with a volume of 266 cc.' 'The diagnosis of these types of tumors is made prenatally by three-dimensional ultrasound, assessing the size of the lesion and its extension.' 'MRI provides additional information on anatomical relationships. It is useful in the differential diagnosis of myelomeningocele and other rare entities such as neuroblastomas, gliomas, hemangiomas, neurofibromas, chordomas, leiomyomas, lipomas, and melanomas, among others.'	Diagnostics • Advocating [early] detection (ultrasound, MRI). • Failures or successes in diagnosis • Emphasizing or presenting diagnostic markers • Clarifying differential diagnosis
49. Use of Cardiac MRI to Assess Antitumor Efficacy of Everolimus in Sporadic Cardiac Rhabdomyoma	'If not fully resected, patients may also require medical therapy to improve their hemodynamics. Everolimus, a mammalian target of rapamycin inhibitor, has shown promise in reducing rhabdomyoma in patients with TSC, but the drug's impact in patients without TSC has not been reported… We report a case of sporadic cardiac rhabdomyoma in a neonate treated with everolimus resulting in tumor regression as documented by cardiac MRI.' 'Everolimus should be carefully monitored in patients with ventricular arrhythmia given the potential for increasing incidence of VT. Everolimus was generally well tolerated and may be considered for use in pediatric patients who present with inoperable, spontaneous cardiac rhabdomyoma and potentially life-threatening cardiac effects.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment
50. Congenital thyroid teratoma in a newborn: Case report from Ethiopia	'Cervical teratoma is a rare congenital disease that constitutes about 1–6% of all pediatric teratoma. Few of these cervical tumors are very rarely located entirely in the thyroid gland which are called thyroid teratomas.' 'Thyroid teratoma is extremely rare and about 41 cases have been reported in the English literature so far. It is usually benign; however, if not treated properly they can lead to death because of large growth and local effect on vital structures like airway compression.' 'We report a case of mature thyroid teratoma in a newborn who presented with progressive neck swelling and respiratory distress since birth.'	Unique Presentation • Uncommon feature (location)
51. Fetal subependymal giant cell astrocytoma: A	'At 9 days of age, the child underwent craniotomy and partial excision of the tumor, followed by a second more extensive operation 13 days later. The	Management • Failures or successes in treatment

case report and review of the literature	patient was subsequently administered mammalian target of rapamycin inhibitor (everolimus).' 'In the latest follow-up MRI, at the age of two, the SEGA remained unchanged. Management of these tumors in neonates is challenging, mainly due to high morbidity and mortality of surgical treatment in these ages.' 'Finally, comprehensive preoperative analysis and meticulous planning of the treatment strategy should be discussed in a multidisciplinary team of pediatric specialists, such as neurosurgeons, neurologists, neuroradiologists, pediatricians, and oncologists.'	• Recommend standardization of perioperative practices
52. Prenatal Exophthalmia Revealing a Postnatal Orbital Teratoma	'We report the case of prenatal exophthalmia discovered by ultrasound exam which turned out to be a teratoma postnatally.' 'Conclusion. A prenatal exophthalmia on fetal ultrasound should make us think of a teratoma, even if it is very rare.' 'Our report has the particularity of showing an exophthalmia that was noticed antenatally through ultrasound exam, so its prenatal diagnosis has been made.' 'Orbital teratoma is an extremely rare congenital pathology; it can be discovered prenatally using ultrasounds. Thereafter, MRI can point to this pathology when showing exophthalmia and allows early treatment of the newborn while sparing the eyeball whenever possible. Otherwise, surgery with mutilations is required with challenges of performing eyeball reconstruction on a growing child.'	Diagnostics • Advocating [early] detection (ultrasound). • Failures or successes in diagnosis • Emphasizing or presenting diagnostic markers • Avoiding misdiagnosis
53. Sacrococcygeal teratoma in one twin: a case report and literature review	'Ultrasonography is an optimal method for prenatal screening and diagnosis of fetal sacrococcygeal teratoma. MRI can be used to assist in the diagnosis. However, sacrococcygeal teratoma in the twin pregnancy is rare.' 'We reported a case of one twin with sacrococcygeal teratoma in dichorionic-diamniotic twin pregnancy. One twin with sacrococcygeal teratoma was diagnosed at the second trimester by ultrasonic examination and another twin was normal.' 'Sacrococcygeal teratoma in twin pregnancy is rare. Early antenatal diagnosis is important. Once the sacrococcygeal teratoma is diagnosed, clinicians should be aware of the associated maternal and fetal complications. Expecting parents should be counseled by the multidisciplinary team about the management and prognosis of the STC twin	Diagnostics • Advocating [early] detection (ultrasound, MRI). • Failures or successes in diagnosis

	and co-twin. Prompt surgical excision of the sacrococcygeal teratoma after birth should be suggested.'	
54. Description of a giant hypothalamic hamartoma associated with an immature ruptured giant sacrococcygeal teratoma: a case report	'Here, we describe an immature ruptured GSCT complicated by hemorrhagic shock at 32-week gestation boy requiring an emergency delivery, followed immediately by urgent surgical removal. A brain lesion resembling a GHH was also present on the antenatal MRI. In order to exclude metastatic immature teratoma or glioma, a biopsy was performed by a retro-sigmoidal approach, which confirmed the nature of the hamartoma. Here, we describe for the first time the association of a ruptured immature GSCT associated with a GHH.' 'For the moment, we have no link between these two rare forms of giant lesions. However, the occurrence of these two uncommon midline abnormalities suggests this is more than coincidence although the combination has not previously been recognized as part of any syndrome. However, one might be established by future genetic studies.'	Rare Case • First Case of (Giant Hypothalamic Hamartoma and Giant Sacrococcygeal Teratoma) in (Neonate) • Landmark
55. Fibrous hamartoma of the thigh in a neonate	'FHI is a benign, soft tissue lesion presenting in early infancy and even the neonatal period that carries diagnostic histopathology and supportive MR imaging and immunostaining that can differentiate this tumor from other pediatric soft tissue masses. However, due to its rarity, it is important to recognize its characteristic diagnostic criteria and ensure its place on the differential diagnosis because it is largely benign and does not warrant aggressive therapy.'	Diagnostics • Emphasizing or presenting diagnostic markers • Avoiding misdiagnosis • Clarifying differential diagnosis
56. Giant High-Grade Immature Teratoma of the Central Nervous System (CNS) in an Infant: A Case Report	'Immature teratomas are extremely rare. CNS teratomas have been known for poor patient prognosis and recovery and also reduce survival. However, chemoradiotherapy has been reported to increase patient survival.' 'Early diagnosis and treatment of immature teratomas are essential in patient prognosis. Chemotherapy is not always needed, but complete surgical removal and patient follow-up are always a necessity. In addition, adequate follow-up of these patients is critical to evaluate their further treatment plan and recurrence risk.' 'Recurrence of these rare tumors should always be considered, and sufficient follow-up is of utmost importance.'	Management • Recommend standardization of perioperative practices • Treatment of an unusual case

57. Successful treatment of neuroblastoma in a newborn baby. [Russian]	'The development of the tumor process in this nosology is based on genetic disorders that may be associated with segmental breakdowns in chromosomes or a change in their number. The presence of aberrations of 1p and 11q loci serves as a criterion for determining the risk group, and amplification of the NMYC oncogene is an indicator of the aggressiveness of the disease.' 'The causes of neuroblastoma formation are not clear. There is no evidence of the influence of unfavorable environmental factors, the presence of occupational hazards in parents, taking medications, smoking and drinking alcohol during pregnancy on the development of the disease' 'The disease begins when a mutation occurs in embryonic neuroblasts, which fail to develop into mature nerve cells of the sympathetic ganglia or adrenal cells, and continue to divide in the absence of differentiation. As the child grows, the likelihood of maturation of mutated neuroblasts decreases, and the risk of tumor formation increases.' 'There is a suggestion that embryonic nerve cells begin to mutate even before the child is born. Characteristic genetic defects in neuroblastoma include the loss of a portion of the short arm of chromosome 1 (1p36), the long arm of chromosome 11 (11q)... ' 'Blood biochemistry was characterized by an increase in the level of alkaline phosphatase to 359 U/L and transaminases (alanine amine - 11.8 U/L; aspartate amine - 124.2 U/L). High levels of tumor process markers were determined: alpha-fetoprotein 6267 IU/ml, NSE >200 μg/L. Tumor cells were not detected in the myelogram.'	Etiology / Pathogenesis • Considering the cause of the disease (genetic factors, environmental factors, epigenetic factors)
58. Successful treatment of non-midline primary malignant germ cell tumors with yolk sac components in neonates: report of 2 cases	'These tumors with yolk sac components, which are thought to have a poor prognosis, were successfully treated with complete tumor resection alone and subtotal tumor resection with chemotherapy, respectively. Event-free survival exceeds 5 years for each patient even though neither received radiotherapy. The authors highlight the role of radical surgery and the successful treatment of neonatal YST with aggressive resection (and chemotherapy in 1 case) while avoiding radiation therapy. They also report the very rare non-midline location of these neonatal NGGCTs…' 'The importance of including NGGCTs in the differential diagnosis of non-midline intracranial tumors in neonates resides in the fact that they can be readily detected noninvasively with serum or CSF AFP, which may change management.'	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Recommend standardization of perioperative practices • Treatment of an unusual case

	‘There is no definitive consensus on treatment of CNS NGGCTs.’ ‘While the extraventricular location of these tumors may have been protective against dissemination, aggressive resection may play a role in good prognosis and can potentially help avoid RT.’	
59. Ultrasound-guided sacral multifidus plane block for analgesia following excision of sacrococcygeal teratoma in two neonates	‘We describe the use of an ultrasound-guided sacral multi dus plane block in two neonates undergoing surgical excision of sacrococcygeal teratoma. The block is technically easy to perform and also avoids traversing critical structures. Hence, it may be regarded as a promising analgesic technique for painful interventions in the sacrococcygeal area.’	Management • Advocating the use of a technique • Failures or successes in treatment
60. A congenital extranasal glioma in a newborn	‘Given advances in modern technology, the prenatal diagnosis of a nasal mass is possible. However, it is important to obtain postnatal imaging to confirm the absence of intracranial connections prior to any biopsy or surgical procedure. In addition, imaging and biopsy samples can assist in differentiating nasal gliomas from other masses such as dermoid cysts, fibrosarcoma, fibroma, rhabdomyoscarcoma, and hemangiomas. For instance, MRI will be helpful with excluding intracranial communications and examining soft tissue, while CT is helpful with examining bony deformities associated with the mass. Furthermore, an ultrasound may assist with determining whether tissue is cystic, solid, or vascular, the latter of which is more commonly associated with hemangiomas.’ ‘In summary, nasal gliomas are rare masses that are usually benign. They are embryologically related to encephaloceles and can have similar appearances to other nasal masses. Thus, imaging and histopathology are paramount in the diagnosis of nasal gliomas.’	Diagnostics • Advocating [early] detection (prenatal diagnosis, postnatal MRI, CT, ultrasound, biopsy). • Avoiding misdiagnosis • Clarifying differential diagnosis
61. A Neonate with Retroperitoneal Mature Cystic Teratoma - A Case Report	‘We report an unusual case of a large retroperitoneal teratoma in a neonate who presented with abdominal distension. Imaging done showed a cystic lesion with calcifications, internal septations and fat dense areas. It was successfully managed by surgical excision, findings of which were consistent with that of a mature cystic teratoma. Despite being rare, we must consider retroperitoneal teratomas as a differential diagnosis of an abdominal mass in a newborn. Early detection and complete surgical excision may be life-saving.’	Diagnostics • Advocating [early] detection (imaging, prenatal ultrasound, CECT). • Failures or successes in diagnosis

	‘Occasionally the tumour may present late, with infection and rupture leading to complications like abscess formation and peritonitis which may be life-threatening. Therefore, early diagnosis becomes imperative and may be life-saving. Imaging plays a vital role in the diagnosis and management of teratomas. Prenatal ultrasound may also provide valuable information for early diagnosis. In our case, prenatal ultrasound was performed, but the final reports were not available. CECT of abdomen aids in determining the location, morphology, extent, relation to great vessels and other adjacent structures, and the benign nature of the tumour as suggested by homogeneity and fat density. Following clinical examination and imaging, differential diagnoses which we considered were namely germ cell tumour, neuroblastoma and nephroblastoma.’ ‘Retroperitoneal teratoma is a rare entity in neonates. Early diagnosis and management can give a favourable outcome. They have distinct imaging findings like teeth, hair, calcifications; which are pathognomonic. Majority of them are benign.’	• Emphasizing or presenting diagnostic markers • Clarifying differential diagnosis
62. An Unusual Lesion of Epignathus with Duplicate Tongue and Ranula in a Neonate	‘We report a rare case of epignathus (oropharyngeal teratoma) in a neonate, who presented with a midline mass covered with skin and multiple hairs protruding from the palate and associated with bifid tongue and ranula. With the characteristic presentation, diagnosis of oropharyngeal teratoma was made and a massive internet search revealed very few reported cases of ‘’Epignathus.’’ ‘This case report emphasizes the rare clinical presentation of the disease and the prenatal diagnosis of such a condition can help in prompt decision making and management.’	Unique Presentation • Uncommon features • (presentation / phenotype)
63. Congenital Epulis. [Spanish]	‘Congenital epulis is a very rare benign tumor. There is no consensus among the authors regarding its pathogenesis and histogenesis. The indicated treatment is surgical exeresis at the time of birth, mainly when it interferes with feeding and breathing. Early diagnosis and timely treatment completely eliminate the lesion and complications associated with this tumor.’ ‘The treatment for congenital epulis is surgical excision at birth, as there are few reports of spontaneous regression of the lesion. Furthermore, it can result in limitations in closing the mouth and difficulties in breathing and feeding, and interfere with the patient's quality of life.’	Management • Recommend standardization of perioperative practices • Treatment of an unusual case

	'In cases of large tumors diagnosed by prenatal ultrasound that compromise ventilation, surgery is performed using the EXIT protocol (ex utero intrapartum technique), which allows for the establishment of the airway while maintaining oxygenation through the uteroplacental circulation.'	
64. Thyroid teratoma in a newborn	'This case illustrates a rare but serious diagnosis that, if not managed in a timely manner, can lead to significant morbidity and mortality. The aim of this report is to present a case of a neonate presenting with airway compromise shortly after birth secondary to a thyroid teratoma.' 'Our case demonstrated the requirement of urgent management including early stabilisation, transfer to a tertiary referral centre with neonatal expertise, multidisciplinary management, and early surgery with perioperative endoscopic airway assessment.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices
65. Coexisting Infantile Hepatic Hemangioma and Hepatoblastoma in a Neonate: A Case Report	'Infantile hepatic hemangioma and hepatoblastoma are the most common benign and malignant tumors of the liver in the neonatal and early childhood periods, respectively. However, the simultaneous occurrence of these 2 tumors in the same liver lesion is very rare. We report a case of a newborn infant diagnosed with a liver mass by ultrasound examination 4 days after birth.' 'To the best of our knowledge, there is no previous case report of concurrent infantile hepatic hemangioma and hepatoblastoma in the same hepatic mass. Herein, we report a case of a liver mass in an infant that was identified during the first week of life and confirmed by pathology as infantile hepatic hemangioma combined with epithelial hepatoblastoma (fetal type).' 'Whether this rare coexistence of 2 tumors is incidental, or has a real correlation with etiology, needs further investigation.'	Rare Case • First Case of (Hepatic Hemangioma and Hepatoblastoma (in the same mass)) in (Neonate) • Landmark
66. Holt-Oram Syndrome with Sacrococcygeal Teratoma - A Rare Association	'Holt-Oram syndrome (HOS) is characterized by upper-limb defects and congenital heart malformation, and its prevalence is very rare. Mature cystic teratoma is the most common tumor seen in neonates and its most common location is sacrococcygeal region.' 'Herein, we reported a male neonate diagnosed with HOS associated with sacrococcygeal teratoma.' 'Patients with SCTs may be also associated with many congenital other abnormalities such as genitourinary system, musculoskeletal system, neurological, cardiovascular system, and pulmonary system. The incidence	Unique Presentation • Uncommon Features (symptoms → associated syndrome / congenital abnormalities)

	of congenital abnormalities associated with this disease is reported to be 12–30% of the patients.' 'The presented patient with HOS had only bilateral hydronephrosis, ostium secundum ASD and VSD, minimal hydrocele, single umbilical artery, and vein according to upper reported abnormalities. Interestingly, the presented patient had left radius and thumb aplasia.' 'Patients with sacrococcygeal teratomas (SCTs) may have multiple and extreme congenital abnormalities; therefore, patients with SCTs should be carefully evaluated clinically, laboratory, and radiologically and it should be also considered that HOS may accompany them.'	
67. Post-auricular teratoma in an HIV-exposed newborn	'We report a case of an HIV-exposed newborn with a congenital teratoma at the post-auricular site who developed an infection. Early intervention by total surgical resection will prevent complications such as infections and malignant transformation. A term baby was delivered spontaneously by an HIV-positive mother who was on her regular medications.' 'We report a case of post-auricular teratoma in an HIV-exposed newborn complicated with a bacterial infection which posed a challenge in a country with limited resources.' 'The association of congenital teratoma with HIV exposure needs to be confirmed with further studies. Ghazi et al. reported a case of rapid growth of a fetal teratoma in an HIV-infected woman and concluded that further research is needed in this area. HIV-associated tumours are recognised to be predominantly lymphocytic and include Hodgkin's lymphoma, non-Hodgkin's lymphoma, Kaposi sarcoma, and others. Its association with teratoma is very rare.'	Etiology / Pathogenesis • Considering the cause of the disease (environmental factors: HIV-exposure)
68. Arrhythmia as the first symptom of neonatal cardiac tumors: Case report	'Newborn male patient with no significant history, in whom a cardiac arrhythmia was detected during the routine physical examination. After the evaluation by Pediatric Cardiology, it was determined that the patient had supraventricular extrasystoles, in addition to multiple intracardiac masses that, due to imaging characteristics, were compatible with rhabdomyomas, so it was determined that the cause of cardiac arrhythmia was the presence of multiple tumors.' 'When arrhythmias are present in the neonatal period, the cause should always be investigated, since, although a large proportion are benign, patients with non-benign arrhythmias have a high mortality and recurrence	Diagnostics • Failures or successes in diagnosis • Emphasizing or presenting diagnostic markers

	rate. In the case presented, the arrhythmia detected during routine examination was key to the early diagnosis of cardiac tumors. Due to the ultrasound characteristics of hyperechogenicity, circumscribed, non-encapsulated, uniform appearance, and ventricular location, these tumors were diagnosed as multiple rhabdomyomas.'	
69. Mature Cystic Teratoma in a Newborn With Down Syndrome	'Due to chromosomal instability, DS is inferred to be a cancer predisposition syndrome. The malignancy pattern in DS is unique with higher incidence of hematological malignancies and solid tumors are rarely reported. Down syndrome neonate was incidentally diagnosed with a retroperitoneal cystic lesion along the left kidney during evaluation for poor feeding on ultrasonography, raising suspicion of an adrenal hemorrhagic cyst.' 'It is also important to understand the distinct neoplasmic profile observed in Down syndrome as it differs widely from a normal neonate.'	Etiology / Pathogenesis • Considering the cause of the disease (genetic factor: Down-syndrome chromosomal instability)
70. Neuroblastoma in a Newborn Female	'This is a case of neuroblastoma in a 4-day-old female managed with surgical resection. This case highlights the potential challenges of diagnosis of retroperitoneal masses on prenatal ultrasound and in newborns and the importance of utilizing available resources when making difficult decisions in management.' 'When diagnosis is straightforward, appropriately selected newborns can often be managed with observation alone. We present a case of neuroblastoma in a newborn female managed with surgical resection due to inconclusive imaging findings.' 'This case highlights the challenges of preoperative and intraoperative decision-making and the importance of utilizing available resources to assist in these difficult situations.'	Management • Failures or successes in treatment • Recommend standardization of perioperative practices
71. Role of pre-operative endovascular embolization of a giant sacrococcygeal teratoma in neonate: a case report	'We present a case of a highly vascular giant SCT in a neonate, which was successfully embolized through an endovascular approach prior to surgery. The femoral artery approach was chosen, with access established using a micropuncture introducer as a sheath. Embolization was performed using a combination of microcoils, Gelfoam slurry, and polyvinyl alcohol particles. The patient developed femoral artery spasm post-procedure, which resolved with the application of a glyceryl trinitrate patch.' 'Conclusions: Performing pre-operative endovascular embolization on a giant sacrococcygeal teratoma presents particular challenges, primarily due	Management • Advocating the use of a technique or treatment • Failures or successes in treatment • Recommend standardization of

	to the difficulty in assessing small vessels and the potential complications associated with this procedure. Nevertheless, this technique proves exceptionally valuable in helping the surgeon minimize blood loss during surgery, thereby reducing the risks of morbidity and mortality. Comprehensive planning for the embolization procedure is essential, encompassing the identification of potential vascular access points and alternatives, along with careful selection of the appropriate catheter.'	perioperative practices

In summary, there were 31 Case Reports that were categorized as Management, 16 as Diagnostics, 12 as Unique Presentation, 8 as Rare Case, and 4 as Etiology / Pathogenesis.

Figure 35: Case Reports by Category

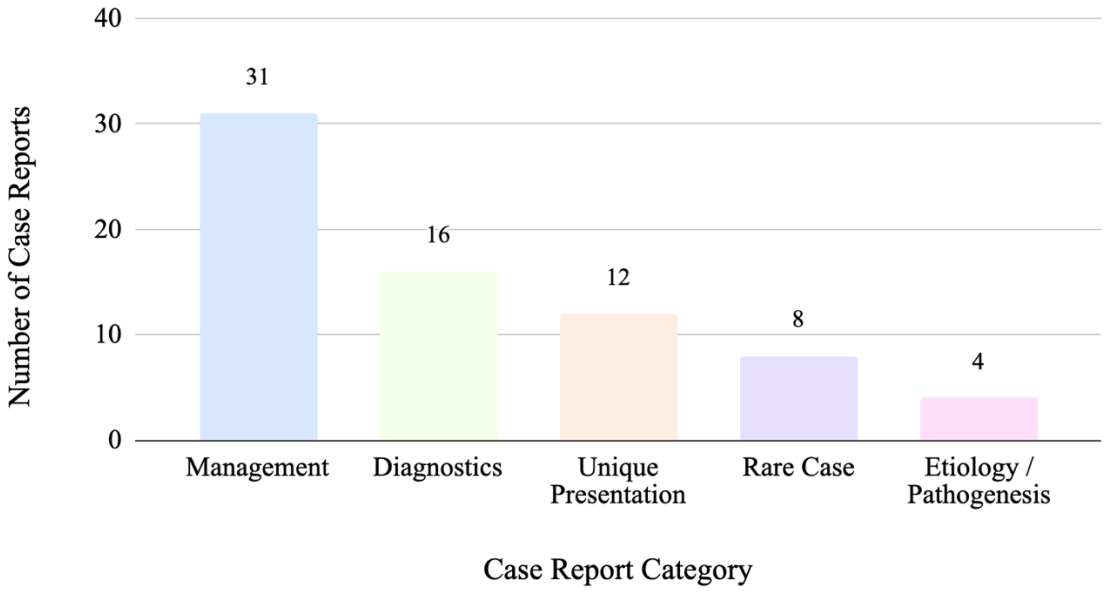


Figure 36 shows a breakdown of Case Reports by Category and Country Income Level. Notably, High Income Countries published the most Management reports. For all other country income levels except for Low Income Countries, this category held the highest number of published Case Reports. The only case reports published in Low Income Countries were in the categories of Unique Presentation and Diagnostics.

Figure 36: Distribution of Case Reports by Category and Country Income Level

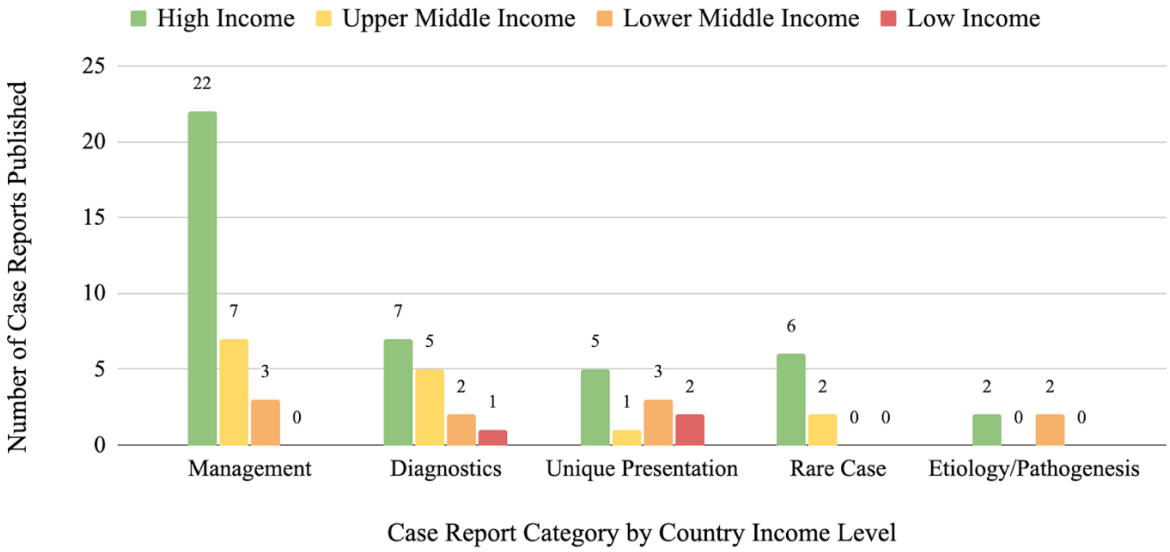
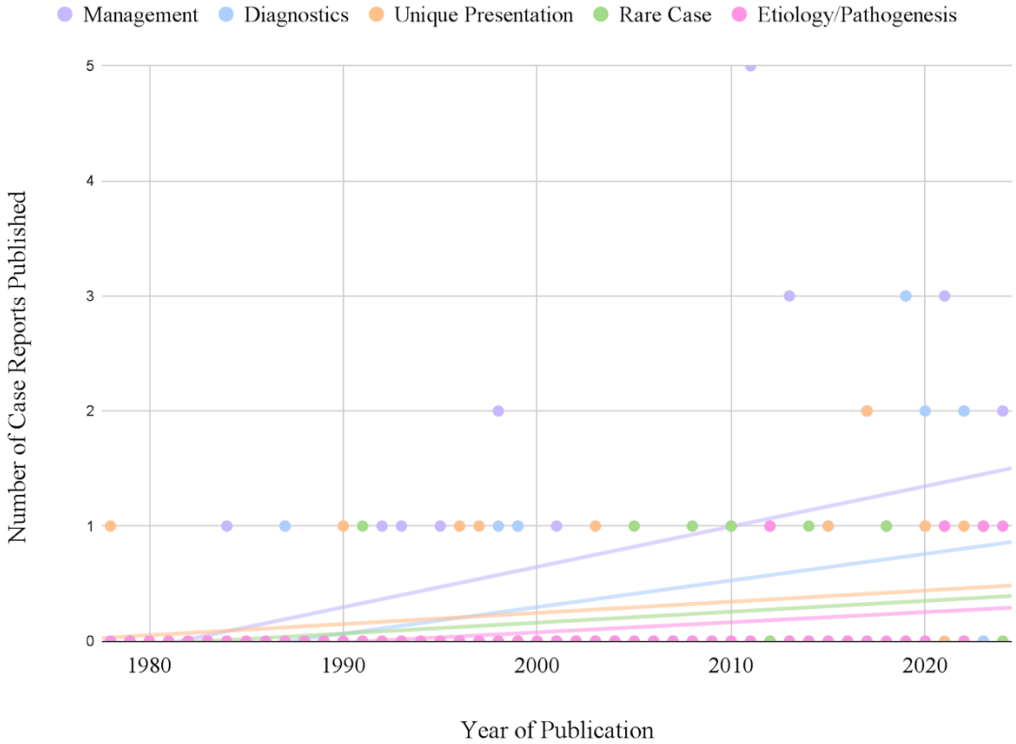


Figure 37 shows the trends of publishing for Case Reports within different categories over the years. Management consistently published with more frequency averaging a slope of m=0.035 reports per year. Diagnostics has a slope of m=0.0231. Unique Presentation (m=9.71E-03), Rare Case (m=9.48E-03), and Etiology/Pathogenesis (m=8.79E-03) have the smallest slopes.

Figure 37: Case Reports by Category over the Years



3.4 Discussion

3.4.1 The Method: Strengths and Limitations

As was made apparent through the systematic review in Chapter 2, there exists a very limited body of literature on Neonatal Tumours. The volume of this material gets even smaller when we limit the scope to research conducted and published in LMICs. Especially when factoring in the strong publication bias in LMICs for publishing positive results which was evident from the results of our systematic review and meta-analysis, it is imperative to explore other avenues of reporting to gain more insight into Neonatal Tumours from a global surgery perspective. Additionally motivating this review of grey literature was the fact that upon initial assessment of the literature there seemed to exist a far larger body of published Case Reports than reviews, which is a relatively unique phenomenon to this patient population and condition.

Reviewing grey literature comes with significant limitations, namely in the stages of searching for and analysing it (Benzies et al., 2006). One article investigating the challenges in reviewing grey literature states that it is 'troublesome to search and locate… because there [are] no central sources, such as libraries or databases, where it [is] collected or housed' (Mahood et al., 2014) Additionally, grey literature tends to be extremely heterogeneous and the differing document lengths, credibility, and formatting create significant challenges during data collection and analysis (Mahood et al., 2014).

Despite these pitfalls, new perspectives argue for the use of grey literature in reviews as a supplement to peer-reviewed literature, especially for reviews that aim to encompass the wide range of existing knowledge on a subject. A study that examined characteristic differences between grey and peer-reviewed literature found that grey literature more evenly balances qualitative, quantitative, and mixed methodological approaches, while peer-reviewed literature is largely biased towards quantitative methods (Yoshida et al., 2024). Perhaps most importantly, the two types of literature 'focused on different continental regions.' 32% of grey-literature documents in their review were from Africa as compared to only 7% of peer-reviewed documents. 42% of grey-literature and 27% of peer-reviewed literature were from Europe and Central Asia, while the Americas (16% grey vs 29% peer-reviewed) and Asia-Pacific (11% grey

vs 37% peer-reviewed) regions were represented strongly in peer-reviewed literature (Yoshida et al., 2024). With these strengths and limitations in mind, this Chapter aims to gain more insight into global care practices for neonatal tumours and to better understand the place of case reports in scientific literature – particularly in terms of their importance in educating the global surgery community about rare and understudied conditions.

Our search strategy, as discussed in Chapter 2, could have been expanded to a larger set of databases to gain a broader scope of literature. The screening of reports, while systematic, was not as thorough as screening for peer-reviewed literature for aforementioned reasons of variability and heterogeneity in reports as well as for the fact that there does not exist a 'Risk of Bias' assessment for Case Reports equivalent to or as comprehensive as the Newcastle-Ottawa Scale for systematic reviews. The Joanna Briggs Institute Critical Appraisal Checklist does not include a grading scale for the strength of Case Reports and ultimately relies on discussion between reviewers.

Perhaps the most glaring limitation of reviewing grey literature is the fact that quantitative statistical analysis is not feasible due to extreme heterogeneity and low generalizability of data that is reported. Nonetheless, we present the data on diagnostics, treatment, and outcomes that was collected and can contribute observations about the type of results that are published. With such limited possibility for quantitative analysis of these Case Reports, the natural next step was to examine this literature qualitatively. More specifically, after a thorough review of methods that exist to review grey literature, it became quite clear that there exists no determined system of categorizing Case Reports. This leaves us with a massive body of literature reporting on a host of diseases and treatment dilemmas with no way to sort through them, and this is not just true for the subject of Neonatal Tumours. For example, if you conduct a search for Case Reports on myocardial infarctions requiring Coronary Artery Bypass Grafting to appraise different surgical techniques, you will spend a significant amount of time parsing through reports focused on genetic markers of heart disease, early diagnosis, or cases that are so unique they have no application to your interests. Data that is already difficult to analyse is almost ineffectual, leaving it just out of reach.

This review, to the best of our knowledge, contains the first developed system for Case Report categorization. Having only piloted this method on one subject specific body of literature, we acknowledge potential limitations to this framework. While future adjustments may be necessary to increase generalizability, this system provides a first step forward for a new place for Case Reports in scientific literature.

3.4.2 Reporting of the Data

As previously discussed, one of the main drawbacks in reviewing grey literature is significant heterogeneity in how data is reported and where it is reported from. This incongruity is apparent in our own review where country income level has a direct relationship to the proportion of case reports. 60.6% of Case Reports in this study were from High Income Countries, 21.1% from Upper Middle Income Countries, 14.1% from Lower Middle Income Countries, and 4.2% from Low Income Countries. With only 3 Case Reports (and 0 peer-reviewed articles in our systematic review) from Low Income Countries, we have gained little to no knowledge on the state of Neonatal Tumour management in these regions of the world. The World Bank estimates that about 9% of the global population resides in Low Income Countries, leaving 3 Case Reports to represent our entire body of knowledge on this disease for almost one tenth of the population (World Bank, n.d.). This lack of literature is even acknowledged in one Case Report from a Low Income Country that was included in our own study, which stated, 'although there is no dearth of literature on SCT, there are very few case series from resource challenged nations like ours,' (Sinha et al., 2013) Additionally, while High Income Countries have been publishing Case Reports on Neonatal Tumours since 1978, the first in our study from a Low Income Country was published in 2017 (Figure 28). For Lower Middle Income Countries this was in 2003 and for Upper Middle Income Countries the first Case Report meeting our inclusion criteria was published in 2008.

This difference is stratified regionally as well. While 16% of the global population resides in Sub-Saharan Africa, only 8.5% of Neonatal Tumour Case Reports were from this region (World Bank, 2025). 26.8% of Case Reports were from Europe and Central Asia, which over-represents the 11.5% of the global population that resides in these regions (World Bank, 2025). In a striking difference, North America's population is almost half the size of the population of Latin America

and the Caribbean, though this region published more than 3 times the amount of Case Reports of the latter (World Bank, 2025).

The question now becomes why are these discrepancies so considerable? There are many barriers to publishing that are particular to Case Reports. One article that discusses the challenges in publishing Clinical Case Reports notes a decline in case report acceptance in academic journals as original research and systematic reviews have a 'higher potential for broader impact and generalizability' which is prized with a current research emphasis on quantifiable data (Kuo 2023). Coupled with a space limitation in print journals and the fact that case reports attract significantly less funding, this makes publishing a considerable challenge. These barriers are only heightened in lower income settings, where researchers face exacerbated financial considerations with limited institutional support. A study investigating the Article Processing Charges (APCs) as a barrier to Open Access publishing reported 'that higher institutional resourcing is associated with researchers publishing in journals with higher APCs' and that researchers with fewer resources are impeded from publishing research as Open Access (Klebel et al., 2023). Simultaneously, researchers in low income and low resource settings often face internal obstacles, as presented by the 2021 Proceedings for the Association for Information Science and Technology (Potnis et al., 2021). The panel identified challenges to conducting and publishing research in developing countries including a 'lack of rigorous training for conducting research,' 'lack of research culture,' 'lack of institutional mechanisms (e.g., review boards) for approving research designs and methodologies,' 'lack of funding opportunities at the institutional, regional, and national levels,' and more (Potnis et al., 2021). Even when Case Report publishing does occur in LMICs, the scope of patients we see is limited to cases that occur in larger district or research hospitals and otherwise urban settings. Cases from local or rural clinics or continue to go unreported, as do those treated by traditional or folk medicine.

These disparities in reporting are extremely important to acknowledge and address for many reasons. Firstly, treatment, management, and diagnostic practices for Neonatal Tumours are not standardized globally, and differ significantly by hospital. Especially in lower income regions, hospitals likely do not have the same capacity, specialized training, or the equipment used for early diagnosis and advanced treatment as in high income regions. While we remain unaware of

the state of Neonatal Tumours in low resource settings, we have no way to estimate the amount of tumours that go undiagnosed, or tumours that are operable yet untreated for lack of knowledge, resources, money, and accessibility. Addressing this lack of reporting will in the future allow us to determine current management practices, educate care practitioners for earlier diagnosis and work towards providing aid, funding, training, and access where needed.

3.4.3 Patient Characteristics and Observations of the Grey Literature

Out of the cases we collected data on, Germ Cell Tumours were the most reported diagnosis comprising 55% of the cases in our dataset. Within this 44 patient category, 16 patients were diagnosed with Sacrococcygeal Teratoma. These observations are in line with results from our systematic review.

As expected, postnatal diagnosis was more commonly reported than antenatal diagnosis. The majority of patients were treated with tumour resection with 69 of 80 cases utilizing tumour resection either alone or with adjuvant treatment. Only 2 patients were treated with Chemotherapy on its own, further confirming that management of this condition is almost entirely surgical.

With only 7 deaths out of 80 patients and 10 reports of complications in surviving patients, we must recognize a high success rate in these Case Reports that is not representative of the true survival rate for this condition (78.6% as estimated in our systematic review). While statistical analysis was not feasible for these reports, we can note an observed bias for publishing cases with positive results. This could be due to the fact that many Case Reports describe success stories to highlight innovative treatments or breakthroughs in management.

3.4.4 A Novel System of Categorization

The most significant feature of this study was the development of a novel system of categorization for Case Reports by what they intended to present. The thematic analysis used to determine these categories was meticulous and informed. One source that was referenced in the decision making process was Guidelines to Writing a Case Report, which cites 5 reasons for writing a case report: ‘1) an unexpected association between diseases or symptoms; 2) an

unexpected event in the course observing or treating a patient; 3) findings that shed new light on the possible pathogenesis of a disease or an adverse effect; 4) unique or rare features of a disease; 5) unique therapeutic approaches; variation of anatomical structures,' (Guidelines to writing a clinical case report, 2017). Taking these into consideration while drawing themes from each report, our final framework resulted in 5 categories of our own, each with their own themes.

The first two categories were relatively straightforward. The category of Management had the main purpose of reporting suggestions or dilemmas in the treatment of a case that might inform future care practices. There were four themes that corresponded to this category:

1) Advocating the use of a technique or treatment
    a) Example: 'For safe management of cases of pharyngeal teratoma, careful preoperative assessment of the airway is most important and sufficient preparation and careful intubation are mandatory to keep airway patent' (Karal et al., 2019)
2) Reporting failures or successes in treatment
    a) Example: 'We report 2 patients of symptomatic MHCW, characterized by progressive respiratory distress, who underwent surgical treatment with prompt resolution of symptoms' (Virgone et al., 2013)
3) Recommending the standardization of perioperative practices
    a) Example: 'For infants or adults a therapeutic strategy similar to that for sacrococcygeal malignant teratomas 22'23 is recommended for malignant cervical teratomas' (Uchiyama et al., 1995)
4) Reporting treatment of an unusual case
    a) Example: 'This report describes a newborn with a large mediastinal teratoma (MT) presenting with severe respiratory distress (RD) at birth…To our knowledge, only 16 newborn infants with MT presenting with RD have been reported' (Kuroiwa et al., 2001)

The category of Diagnostics had the purpose of reporting suggestions or dilemmas in the diagnosis of a case to inform future practices. Themes corresponding to this category were:

1) Advocating for early detection or a diagnostic technique

    a) Example: Prenatal diagnosis is essential given the risk of respiratory distress' (Rami et al., 2012)
2) Reporting failures or successes in diagnosis
    a) Example: 'We present a case of epignathus teratoma detected during obstetrical ultrasound screening. Diagnosis enabled planning for a safe delivery in a suitable multidisciplinary unit and use of the EXIT procedure.' (Ferrer et al., 2025)
3) Emphasizing or presenting diagnostic markers for consideration
    a) Example: 'When arrhythmias are present in the neonatal period, the cause should always be investigated, since, although a large proportion are benign, patients with non-benign arrhythmias have a high mortality and recurrence rate' (Ramírez-Terán, 2024)
4) Avoiding misdiagnosis of a disease
    a) Example: 'Mesenchymal hamartoma may be misdiagnosed with enchondroma, fibrous hamartoma, malignant mesenchymoma, and aneurysmal bone cyst. We can achieve definitive diagnosis only by resorting to histopathological examinations' (Amouei et al., 2019)
5) Clarifying differential diagnosis of a disease or subtype of a disease
    a) Example: 'MRI provides additional information on anatomical relationships. It is useful in the differential diagnosis of myelomeningocele and other rare entities such as neuroblastomas, gliomas, haemangiomas, neurofibromas, chordomas, leiomyomas, lipomas, and melanomas, among others' (López-Franco et al., 2019)

The next two categories, upon first glance, seem almost interchangeable. In practice, however, they address two distinct features of case reports. The Unique Presentation category encompasses reports with the main purpose of raising awareness for a specific phenotype or presentation of the disease that might not be easily recognized. Corresponding to this category is the theme:

1) Reporting uncommon features, including everything from uncommon symptoms, unusual comorbidities or associations, or rare locations or manifestations of the disease in the body.

a) Example: ‘Occurrence of teratomas at the lumbar area is a rare anatomical anomaly and its association with dysraphysm is rarely described. Here we report 2 cases; the first skin covered and the second multicystic lumbar mass with dural extension and spinal dysraphysm’ (Tihitena et al., 2017)

On the other hand, the category of Rare Case has the distinct purpose of documenting a landmark case, specifically when the case is the first of its kind reported in the literature. The theme of this category follows a specific framework:

1) The first documented case of (diagnosis x) in (population of interest y), where the population of interest can include a demographic group, a patient population, or a region
    a) Example: ‘This tumour appears to be the first meningeal haemangiopericytoma described in a newborn’ (Aouad et al., 1991)

Finally, the category of Etiology / Pathogenesis includes reports with the ain purpose of proposing further investigation into a particular origin of or contributing factor to the disease. The corresponding themes to this category are:

1) Considering the cause of the disease (e.g. genetic factors, environmental factors, epigenetic factors, etc.)
    a) Example: ‘Due to chromosomal instability, DS is inferred to be a cancer predisposition syndrome. The malignancy pattern in DS is unique with higher incidence of hematological malignancies and solid tumors are rarely reported.’ (Poyyamozhy et al., 2024)
2) Considering the how a specific phenotype/subset of the disease arises
    a) Example: ‘We have reported a case of sacrococcygeal teratoma with a retina-like structure in a newborn and suggested the importance of blood supply and oxygen circumstance in the formation of the stratified structure’ (Takamatsu, 2012)

Occasionally, reports were somewhat difficult to categorize because they met themes for multiple categories and required extensive discussion. While a report might touch on two or three different points from different categories, ultimately decisions were made based on what

the majority of content in the report was focused on, specifically considering the content of the discussion and the main takeaways as acknowledged in the title, abstract, and conclusion.

The vast majority (43.7%) of Case Reports fell into the category of Management. With such a rare ailment, reports detailing the course of treatment and offering suggestions for future cases are extremely valuable, so this distribution is not surprising. The next largest category was Diagnostics, comprising 22.5% of Neonatal Tumour Case Reports, which often advocated for prenatal screening and earlier diagnosis for successful results. 16.9% of cases reported Unique Presentations of Neonatal Tumours, particularly with focuses on uncommon locations of the tumour in the body, symptoms such as hyperkalaemia, or associations with other diseases such as foetal hydrops. 11.3% were categorized as reporting Rare Cases, which were differentiated from cases about Unique Presentation because of the importance in keeping track of landmark cases. Especially for rare diseases it can be useful to track the first reported cases of a specific type within a population for learning about how these cases might be diagnosed and managed. The category with the fewest Neonatal Tumour reports was Etiology / Pathogenesis (5.6%). Three of these reports presented possible causes of the disease (Genetic disorders, HIV-exposure, and Down Syndrome) and one presented causes for a subtype of the disease (blood supply and oxygen circumstance for the formation of retina-like structures).

It is quite difficult to make inferences about the relationship between country income level and type of case reports that are published, as very few case reports are published outside of High Income Countries. However, when examining publishing trends of Case Reports by category, there are several details of note. There are no negative trends which tells us that more Case Reports are being published in general, and the trend with the highest slope is for Case Reports about Management. We might infer that globally, we are learning new and effective ways to manage Neonatal Tumours as science and medicine advance; this data also suggests that care providers prioritize reporting suggestions to inform future practices above other types of reporting when writing Case Reports. We can also note that publishing trends for Case Reports about Unique Presentation and Rare Cases have similarly small slopes. The logical reasoning for this is that as more literature is published on Neonatal Tumours, the emergence of new phenomena reported in the literature is not expeditious and, in all likelihood, will plateau over

time. As for Etiology / Pathogenesis, the publishing trend for this group has the smallest slope. This suggests that authors or publishers consider contemplating the cause of the disease to be less urgent or impactful than reporting on diagnosis or treatment, at least for a disease that is so rare, often emergent, and difficult to treat.

3.4.5 Contribution to the Field

Case Reports have long been a valuable source of learning and an integral part of clinical research and literature. Particularly for the field of global surgery, for future standardization of medical practices, and for reducing outcome disparities across healthcare settings around the world, case reports provide a critical resource for this medical education. This review pilots, to the best of our knowledge, the first systematic method of categorizing Case Reports through thematic analysis. Not only does this system make this literature more amenable by providing a comprehensive organizational foundation for a previously disordered body of work, but it also underscores the multifold value of this material. In this review, we present five distinct categories of Case Reports and the important purposes each of them serves. Specifically, for each of these categories we provide evidence for a research need to fill gaps in the literature where care practices and outcomes are underreported in lower resource settings; furthermore, we highlight the importance of grey literature in particular for understanding conditions that are rare and understudied. Though further work is needed to test the robustness and generalizability of our novel method on grey literature pertaining to other diseases, the hope is that in the future this system can be used universally to categorize Case Reports so they can be readily and efficiently utilized for medical education.

Chapter 4: Conclusion

As Neonatal Tumours in their rarity and complex presentations pose such an interesting surgical dilemma, there are several questions we must consider to advance our knowledge of this condition, especially given the findings of our two studies.

While our systematic review yields no definitive conclusions about Lower Income Countries, this project has determined that Neonatal Tumour patients have significantly lower survival odds in Upper Middle Income Countries as compared to High Income Countries, and that Surgical Mortality in High Income Countries is significantly lower than in Upper Middle Income Countries. In review of these disparities, we must ask how we might improve outcomes for patients with Neonatal Tumours in LMICs? Specifically, how can we improve antenatal diagnosis in LMICs? As previously discussed, LMICs are lacking in both specialists and accessibility required to treat these conditions. Therefore, we should first focus on training midwives to use techniques such as ultrasound and prenatal MRI to improve early detection in areas where specialists are not available. Additionally, we can increase the frequency antenatal diagnosis by improving accessibility in rural areas; this can be achieved through providing funding for travel to receive prenatal scans and building more clinics. Finally, we must work towards educating the parents on the importance of early detection for preventing and treating possible birth defects or complications.

Outside of our quantitative conclusions, we have observed an extreme lack of publication in LMICs as well as a bias for publishing positive results. So how might we improve data collection worldwide? Firstly, we must address the lack of administrative resources for data collection: namely, increasing staffing numbers, establishing databases for data collection, and to standardize an efficient and comprehensive system for reporting. These standards should include adequate reporting of presentation, diagnosis, treatment, and outcomes. The final piece to improving data collection is improving follow up for Neonatal Tumour patients post discharge so outcomes can be thoroughly reported. This can be achieved through educating parents on the importance of follow up and increasing accessibility to follow-up services. Finally, we must ask how we might support publication in LMICs? This can be achieved through three methods:

increasing research funding, supporting international collaborations, and training more doctors and medical staff. The most reported barrier to publishing in LMICs is time, so by training more care practitioners, the burden of care on each physician can be reduced, allowing them more time to pursue research.

One other possible method for making data collection easier in LMICs is to establish national tumour registries for Neonatal Tumours. These registries would allow for systematic collection and management of data including diagnosis, treatment, and follow up for patients with Neonatal Tumours. Establishing national registries for Neonatal Tumours would makes data reporting much easier, therefore improving access to data from low-income regions of the world.

Future work includes expanding the search of reviews pertaining to Neonatal Tumours to more databases to find data that might have been missed. Additionally, a future systematic review would include comparing survival between treatment methods in a statistically reliable way, as within our systematic review, we did not have enough cases reporting the use of Chemotherapy to compare mortality by treatment method in a way that accurately represents actual risk of death in the Neonatal Population. For future work with grey literature, we hope that our system for categorizing Case Reports can be further tested. Eventually, there could be largescale reviews of Case Reports done for every major condition to categorize reports and document observations from this bank of literature. In the future, reports could possibly be even categorized before publication to make searching for a certain category of reports within a subject easier. This could help to further increase accessibility and usefulness of these reports in larger reviews or in medical education.

Finally, to return our focus to the subject of this review, in the near future I will be conducting a qualitative study to analyze parental perspectives on Neonatal Tumours. The purpose of this study will be to investigate the psychological impacts on parents of having a child diagnosed with a Neonatal Tumour, as well as to further explore accessibility to treatment as it differs across country income level. We have already received ethics approval for this study through Quality Improvement and have conducted 16 total interviews with 10 parents from Muhimbili, Tanzania and 6 parents from Oxford, UK. These parents were approached using purposive

sampling and interviewed for 30 minutes with questions about general diagnosis and accessibility to treatment, the psychological impacts of their experience, long-term impacts on their parenting, and how support and resources for parents in the NICU might be improved. Analysis using a hybrid reflexive thematic approach and dual coding is currently underway.

This project has reiterated the importance of reporting in LMICs for the improvement of global health and has demonstrated severe disparities in outcomes for Neonatal Tumours across country income level. I hope that this work will eventually bring about a newfound appreciation for Case Reports in medical literature, especially for educational purposes, and that the topic of Neonatal Tumours gains more attention from the global surgery community so that one day, these discrepancies we've illuminated might be remedied.

Appendix

Table 37: Pairwise Z-Tests for Survival Rate Differences (Country Income Level)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
High Income vs. Upper Middle Income	0.0267	0.0802
High Income vs. Lower Middle Income	0.0000077	0.0000232
Upper Middle vs. Lower Middle Income	0.00000021	0.0000006

Table 38: Pairwise Z-Tests for Survival Rate Differences (Tumour Type)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
CNS Tumour vs Germ Cell Tumour (GCT)	1.20E-22	3.36E-21
CNS Tumour vs Hepatoblastoma	0.68213783	1
CNS Tumour vs Neuroblastoma	2.03E-14	5.70E-13
CNS Tumour vs Other	5.59E-05	0.00156519
CNS Tumour vs Renal Tumour	0.00514648	0.14410153
CNS Tumour vs Retinoblastoma	4.64E-05	0.00129897
CNS Tumour vs Soft Tissue Tumour	5.71E-05	0.00159895
Germ Cell Tumour (GCT) vs Hepatoblastoma	1.88E-18	5.27E-17
Germ Cell Tumour (GCT) vs Neuroblastoma	0.01217136	0.34079801
Germ Cell Tumour (GCT) vs Other	0.85955611	1

Germ Cell Tumour (GCT) vs Renal Tumour	0.00095726	0.02680316
Germ Cell Tumour (GCT) vs Retinoblastoma	0.91274736	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	6.60E-14	1.85E-12
Hepatoblastoma vs Neuroblastoma	5.21E-12	1.46E-10
Hepatoblastoma vs Other	4.63E-05	0.00129613
Hepatoblastoma vs Renal Tumour	0.00388073	0.10866044
Hepatoblastoma vs Retinoblastoma	4.03E-05	0.00112816
Hepatoblastoma vs Soft Tissue Tumour	0.00014068	0.00393892
Neuroblastoma vs Other	0.41790168	1
Neuroblastoma vs Renal Tumour	0.03798372	1
Neuroblastoma vs Retinoblastoma	0.54553526	1
Neuroblastoma vs Soft Tissue Tumour	1.11E-06	3.10E-05
Other vs Renal Tumour	0.07110946	1
Other vs Retinoblastoma	0.83446246	1
Other vs Soft Tissue Tumour	0.02828101	0.79186817
Renal Tumour vs Retinoblastoma	0.09004496	1
Renal Tumour vs Soft Tissue Tumour	0.8266109	1
Retinoblastoma vs Soft Tissue Tumour	0.03323132	0.93047692

Table 39: Pairwise Z-Tests for Malignancy Mortality (Country Income Level)

Comparison	**Raw P-Value**	**Bonferroni Adjusted P-Value**
High Income vs Upper Middle Income	0.79	1
High Income vs Lower Middle Income	< 0.001	0.003

Upper Middle Income vs Lower Middle	< 0.001	0.003

Table 40: Pairwise Z-Tests for Malignancy Mortality (Tumour Type)

Comparison	**Raw P-Value**	**Bonferroni Adjusted P-Value**
CNS Tumour vs Germ Cell Tumour (GCT)	2.22E-24	6.21E-23
CNS Tumour vs Hepatoblastoma	0.32953747	1
CNS Tumour vs Neuroblastoma	4.21E-14	1.18E-12
CNS Tumour vs Other	0.00018394	0.00515035
CNS Tumour vs Renal Tumour	3.64E-06	0.00010202
CNS Tumour vs Retinoblastoma	0.00261724	0.0732828
CNS Tumour vs Soft Tissue Tumour	0.11390245	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	4.93E-16	1.38E-14
Germ Cell Tumour (GCT) vs Neuroblastoma	0.02264149	0.63396168
Germ Cell Tumour (GCT) vs Other	0.47302909	1
Germ Cell Tumour (GCT) vs Renal Tumour	0.94534658	1
Germ Cell Tumour (GCT) vs Retinoblastoma	0.07709193	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	4.34E-41	1.21E-39
Hepatoblastoma vs Neuroblastoma	4.51E-09	1.26E-07
Hepatoblastoma vs Other	0.00299046	0.083733
Hepatoblastoma vs Renal Tumour	0.00014706	0.0041178
Hepatoblastoma vs Retinoblastoma	0.02476299	0.69336382
Hepatoblastoma vs Soft Tissue Tumour	0.78394174	1
Neuroblastoma vs Other	0.95363028	1

Neuroblastoma vs Renal Tumour	0.47337135	1
Neuroblastoma vs Retinoblastoma	0.39316181	1
Neuroblastoma vs Soft Tissue Tumour	2.76E-21	7.74E-20
Other vs Renal Tumour	0.63477495	1
Other vs Retinoblastoma	0.52356941	1
Other vs Soft Tissue Tumour	0.00121715	0.03408021
Renal Tumour vs Retinoblastoma	0.2437339	1
Renal Tumour vs Soft Tissue Tumour	2.10E-05	0.00058815
Retinoblastoma vs Soft Tissue Tumour	0.01617355	0.45285948

Table 41: Pairwise Z-Tests for Preoperative Mortality (Country Income Level)

Comparison	p-value
High Income vs Lower Middle Income	0.0100
High Income vs Upper Middle Income	0.6754
Lower Middle Income vs Upper Middle Income	0.0176

Table 42: Pairwise Z-Tests for Preoperative Mortality (Tumour Type)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
CNS Tumour vs Germ Cell Tumour (GCT)	1.22E-16	3.42E-15
CNS Tumour vs Hepatoblastoma	0.32008187	1
CNS Tumour vs Neuroblastoma	2.38E-05	0.00066764
CNS Tumour vs Other	0.02969562	0.83147729
CNS Tumour vs Renal Tumour	0.01270156	0.35564362

CNS Tumour vs Retinoblastoma	0.39422857	1
CNS Tumour vs Soft Tissue Tumour	0.04862209	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	4.23E-12	1.18E-10
Germ Cell Tumour (GCT) vs Neuroblastoma	1.14E-05	0.00031798
Germ Cell Tumour (GCT) vs Other	0.58006858	1
Germ Cell Tumour (GCT) vs Renal Tumour	0.27989898	1
Germ Cell Tumour (GCT) vs Retinoblastoma	4.67E-05	0.00130848
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	1.06E-10	2.96E-09
Hepatoblastoma vs Neuroblastoma	0.00019445	0.00544453
Hepatoblastoma vs Other	0.00795585	0.22276372
Hepatoblastoma vs Renal Tumour	0.00340933	0.09546129
Hepatoblastoma vs Retinoblastoma	0.13254291	1
Hepatoblastoma vs Soft Tissue Tumour	0.02300765	0.64421431
Neuroblastoma vs Other	0.57166344	1
Neuroblastoma vs Renal Tumour	0.63884471	1
Neuroblastoma vs Retinoblastoma	0.10244403	1
Neuroblastoma vs Soft Tissue Tumour	0.01604105	0.4491494
Other vs Renal Tumour	0.85493891	1
Other vs Retinoblastoma	0.16814993	1
Other vs Soft Tissue Tumour	0.20091387	1
Renal Tumour vs Retinoblastoma	0.14699228	1
Renal Tumour vs Soft Tissue Tumour	0.16028711	1
Retinoblastoma vs Soft Tissue Tumour	0.69185754	1

Table 43: Pairwise Z-Tests for Treatment Related Mortality (Country Income Level)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
High Income vs Upper Middle Income	0.0044	0.0044

Table 44: Pairwise Z-Tests for Treatment Related Mortality (Tumour Type)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
CNS Tumour vs Germ Cell Tumour (GCT)	0.74322761	1
CNS Tumour vs Hepatoblastoma	0.26848132	1
CNS Tumour vs Neuroblastoma	0.44230072	1
CNS Tumour vs Other		
CNS Tumour vs Renal Tumour	0.43909761	1
CNS Tumour vs Retinoblastoma		
CNS Tumour vs Soft Tissue Tumour	0.60920813	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	0.01403677	0.39302947
Germ Cell Tumour (GCT) vs Neuroblastoma	0.01510415	0.42291623
Germ Cell Tumour (GCT) vs Other	0.75927163	1
Germ Cell Tumour (GCT) vs Renal Tumour	0.11905557	1
Germ Cell Tumour (GCT) vs Retinoblastoma	0.53313016	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	0.36240282	1
Hepatoblastoma vs Neuroblastoma	0.46114645	1

Hepatoblastoma vs Other	0.29938691	1
Hepatoblastoma vs Renal Tumour	0.59912621	1
Hepatoblastoma vs Retinoblastoma	0.03899181	1
Hepatoblastoma vs Soft Tissue Tumour	0.16851829	1
Neuroblastoma vs Other	0.4722289	1
Neuroblastoma vs Renal Tumour	0.972334	1
Neuroblastoma vs Retinoblastoma	0.14520145	1
Neuroblastoma vs Soft Tissue Tumour	0.29010877	1
Other vs Renal Tumour	0.46871658	1
Other vs Retinoblastoma		
Other vs Soft Tissue Tumour	0.63244616	1
Renal Tumour vs Retinoblastoma	0.14531553	1
Renal Tumour vs Soft Tissue Tumour	0.48763896	1
Retinoblastoma vs Soft Tissue Tumour	0.33199679	1

Table 45: Pairwise Z-Tests for Surgical Mortality (Country Income Level)

Comparison	**Raw P-Value**	**Bonferroni Adjusted P-Value**
High Income vs Upper Middle Income	0.0000	0.0000
High Income vs Lower Middle Income	0.0126	0.0378
Upper Middle Income vs Lower Middle Income	0.0000	0.0001

Table 46: Pairwise Z-Tests for Surgical Mortality (Tumour Type)

Comparison	**Raw P-Value**	**Bonferroni Adjusted P-Value**

CNS Tumour vs Germ Cell Tumour (GCT)	0.03587769	1
CNS Tumour vs Hepatoblastoma	0.16211116	1
CNS Tumour vs Neuroblastoma	0.02583658	0.72342432
CNS Tumour vs Other	0.01967675	0.55094891
CNS Tumour vs Renal Tumour	0.02550754	0.7142112
CNS Tumour vs Retinoblastoma	0.01873251	0.52451026
CNS Tumour vs Soft Tissue Tumour	0.15617032	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	7.49E-20	2.10E-18
Germ Cell Tumour (GCT) vs Neuroblastoma	0.65431677	1
Germ Cell Tumour (GCT) vs Other	0.33854922	1
Germ Cell Tumour (GCT) vs Renal Tumour	0.38252633	1
Germ Cell Tumour (GCT) vs Retinoblastoma	0.23148476	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	0.08706221	1
Hepatoblastoma vs Neuroblastoma	1.46E-16	4.09E-15
Hepatoblastoma vs Other	1.60E-06	4.49E-05
Hepatoblastoma vs Renal Tumour	3.37E-06	9.43E-05
Hepatoblastoma vs Retinoblastoma	4.65E-05	0.001302
Hepatoblastoma vs Soft Tissue Tumour	3.35E-10	9.37E-09
Neuroblastoma vs Other	0.4182588	1
Neuroblastoma vs Renal Tumour	0.46576776	1
Neuroblastoma vs Retinoblastoma	0.26155608	1
Neuroblastoma vs Soft Tissue Tumour	0.07505859	1
Other vs Renal Tumour	0.95740309	1

Other vs Retinoblastoma	0.45894378	1
Other vs Soft Tissue Tumour	0.14741648	1
Renal Tumour vs Retinoblastoma	0.44189904	1
Renal Tumour vs Soft Tissue Tumour	0.17493049	1
Retinoblastoma vs Soft Tissue Tumour	0.13547728	1

Table 47: Pairwise Z-Tests for Mortality due to Metastasis (Country Income Level)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
High Income vs Lower Middle Income	0.04188361	0.12565083
High Income vs Upper Middle Income	0.36472588	1
Lower Middle Income vs Upper Middle Income	0.01852639	0.05557918

Table 48: Pairwise Z-Tests for Mortality due to Metastasis (Tumour Type)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
CNS Tumour vs Germ Cell Tumour (GCT)	0.46923512	1
CNS Tumour vs Hepatoblastoma	0.22679181	1
CNS Tumour vs Neuroblastoma	0.41133291	1
CNS Tumour vs Other	0.51029356	1
CNS Tumour vs Renal Tumour	0.51667487	1
CNS Tumour vs Retinoblastoma		
CNS Tumour vs Soft Tissue Tumour	0.16383568	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	0.28814821	1
Germ Cell Tumour (GCT) vs Neuroblastoma	0.43076858	1
Germ Cell Tumour (GCT) vs Other	0.86138072	1
Germ Cell Tumour (GCT) vs Renal Tumour	0.8379363	1
Germ Cell Tumour (GCT) vs Retinoblastoma	0.3871063	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	3.33E-05	0.0009322
Hepatoblastoma vs Neuroblastoma	0.42884497	1

Hepatoblastoma vs Other	0.35922138	1
Hepatoblastoma vs Renal Tumour	0.34618423	1
Hepatoblastoma vs Retinoblastoma	0.15032346	1
Hepatoblastoma vs Soft Tissue Tumour	0.82953631	1
Neuroblastoma vs Other	0.67477292	1
Neuroblastoma vs Renal Tumour	0.65273507	1
Neuroblastoma vs Retinoblastoma	0.32630245	1
Neuroblastoma vs Soft Tissue Tumour	0.00238018	0.06664503
Other vs Renal Tumour	0.98290079	1
Other vs Retinoblastoma	0.43189745	1
Other vs Soft Tissue Tumour	0.1194205	1
Renal Tumour vs Retinoblastoma	0.43883222	1
Renal Tumour vs Soft Tissue Tumour	0.11065696	1
Retinoblastoma vs Soft Tissue Tumour	0.09692333	1

Table 49: Pairwise Z-Tests for Postoperative Survival (Country Income Level)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
High Income vs Upper Middle Income	1.20E-05	3.61E-05
High Income vs Lower Middle Income	0.01259387	0.0377816
Upper Middle Income vs Lower Middle Income	2.21E-05	6.62E-05

Table 50: Pairwise Z-Tests for Postoperative Survival (Tumour Type)

Comparison	Raw P-Value	Bonferroni Adjusted P-Value
CNS Tumour vs Germ Cell Tumour (GCT)	0.03587769	1
CNS Tumour vs Hepatoblastoma	0.16211116	1
CNS Tumour vs Neuroblastoma	0.02583658	0.72342432
CNS Tumour vs Other	0.78541264	1
CNS Tumour vs Renal Tumour	0.02550754	0.7142112

CNS Tumour vs Retinoblastoma	0.01873251	0.52451026
CNS Tumour vs Soft Tissue Tumour	0.15617032	1
Germ Cell Tumour (GCT) vs Hepatoblastoma	7.49E-20	2.10E-18
Germ Cell Tumour (GCT) vs Neuroblastoma	0.65431677	1
Germ Cell Tumour (GCT) vs Other	1.51E-07	4.24E-06
Germ Cell Tumour (GCT) vs Renal Tumour	0.38252633	1
Germ Cell Tumour (GCT) vs Retinoblastoma	0.23148476	1
Germ Cell Tumour (GCT) vs Soft Tissue Tumour	0.08706221	1
Hepatoblastoma vs Neuroblastoma	1.46E-16	4.09E-15
Hepatoblastoma vs Other	0.06120343	1
Hepatoblastoma vs Renal Tumour	3.37E-06	9.43E-05
Hepatoblastoma vs Retinoblastoma	4.65E-05	0.001302
Hepatoblastoma vs Soft Tissue Tumour	3.35E-10	9.37E-09
Neuroblastoma vs Other	4.67E-07	1.31E-05
Neuroblastoma vs Renal Tumour	0.46576776	1
Neuroblastoma vs Retinoblastoma	0.26155608	1
Neuroblastoma vs Soft Tissue Tumour	0.07505859	1
Other vs Renal Tumour	0.00174844	0.04895622
Other vs Retinoblastoma	0.00489311	0.13700708
Other vs Soft Tissue Tumour	0.00054495	0.01525866
Renal Tumour vs Retinoblastoma	0.44189904	1
Renal Tumour vs Soft Tissue Tumour	0.17493049	1
Retinoblastoma vs Soft Tissue Tumour	0.13547728	1

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