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Review Article

Management and Outcomes of Hepatoblastoma in Patients With Trisomy 18: A Systematic Review and Pooled Analysis of 70 Patients

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ABSTRACT

Introduction: Predicted 1-year survival of children with trisomy 18 (T18) has increased to 59.3%. We aimed to systematically review the characteristics, management, and outcomes of children with T18 and hepatoblastoma.

Methods: A systematic literature review of the PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases was performed according to the PRISMA 2020 statement (end-of-search date: 03/03/2024).

Results: Fifty studies reporting on 70 patients were included. The median age at diagnosis was 11.5 months, 85.9% were female (n = 55/64), and 15.0% had mosaic T18 (n = 6/40). Diagnosis was made during symptom evaluation (most commonly hepatomegaly or abdominal mass) in 45.5% (n = 15/33), incidentally in 24.2% (n = 8/33), during surveillance with abdominal ultrasound in 18.2% (n = 6/33), and at autopsy in 12.1% (n = 4/33). The median tumor size was 6.4 cm, 33.3% had multiple tumors (n = 14/42), and metastasis was present in one patient (3.8%; n = 1/26). Neoadjuvant chemotherapy was administered in 42.6% (n = 26/61) and adjuvant chemotherapy in 31.6% (n = 18/57). Surgical treatment was performed in 64.2% (n = 43/67). Of the patients not diagnosed on autopsy, overall mortality was 35.5% (n = 22/62) over a median follow-up of 11.0 months. Among the 26 deceased patients (including those diagnosed on autopsy), the most common causes of death were cardiopulmonary disease (38.5%, n = 10/26) and tumor progression (30.8%, n = 8/26).

Conclusions: T18 does not preclude resection with curative intent for hepatoblastoma. Combination of surgery and chemotherapy should be considered in children on an individualized basis depending on tumor characteristics and underlying cardiopulmonary comorbidities. Locoregional modalities may have a role in the setting of severe comorbidities.

Level of Evidence: Level IV evidence.

1. Introduction

Trisomy 18 (T18), also known as Edwards syndrome [1], is the second most common constitutional autosomal syndrome after trisomy 21, occurring in 1/6000 to 1/8000 live births. It is characterized by both major and minor malformations of the cardiovascular, nervous, gastrointestinal, genitourinary, musculoskeletal or other systems, growth deficiency, and marked psychomotor and cognitive impairment [2,3]. Due to these malformations, T18 is associated with short life expectancy with historically about 50%

Abbreviations: AFP, alpha-fetoprotein; C5V, cisplatin/5-fluorouracil/vincristine; CDDP, cisplatin; IQR, interquartile range; PRETEXT, PRE-Treatment EXTent of tumor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; T18, Trisomy 18.

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living longer than 1 week and 5–10% surviving beyond the first year [4,5].

The unique predisposition for solid organ tumor development associated with T18 was unclear until recently. There has been an increase in life expectancy with 1-year survival increasing from 34.5% between 2008 and 2012 to 59.3% between 2013 and 2017 [6] due to improvements in intensive care and treatment of underlying abnormalities, especially cardiac disease [7]. Due to this longer life expectancy, it is now known that T18 is associated with an increased risk for embryonal tumors, including hepatoblastoma, the most common pediatric liver malignancy that associates with upregulation in SMAD4, TGFβ, and canonical WNT signaling pathways [7–9]. Management of hepatoblastoma is primarily comprised of surgical treatment and chemotherapy, with surgical management required for long-term survival [10]. Risk-adapted management is warranted in T18 since there is an increased risk of morbidity and mortality due to the physical disposition and multiple associated cardiopulmonary comorbidities. Although several reports of hepatoblastoma management in the setting of T18 have been published, no systematic review has been performed to clearly define the presentation, management, and outcomes in these patients.

Therefore, we aimed to perform a systematic review to describe the demographic and clinical characteristics, management, and outcomes of patients with hepatoblastoma and T18.

2. Methods

2.1. Study design and inclusion/exclusion criteria

This systematic review of the literature followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement (Supplemental File 1) [11] and registered in PROSPERO (record number: CRD42023463151). Because this is a systematic review of already published studies, no human subjects are involved, and thus Institutional Review Board approval or patient consent were not required.

Eligible articles were original studies or abstracts that reported on demographic, clinical characteristics, management, and outcomes of children (<18 years) with hepatoblastoma in the setting of T18. Studies were excluded if they focused on basic science or were secondary non-original articles (e.g., reviews, book chapters, editorials, perspectives, commentary, errata, and letters to the editor) without reporting any primary clinical patient data. When studies with overlapping populations or shared patients were encountered, either the most recent, the one reporting the largest number of patients, or providing the highest quality of data was included. In case several articles reported additional data on the same patients, data were extracted from all studies when possible. When other review articles provided data on included studies, we extracted data from these reviews as available. No publication date, language, sample size restrictions or any other search filters were used.

2.2. Literature search strategy

Eligible studies were identified through a systematic search of the MEDLINE (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library databases (end-of-search date: 03/03/2024) using the following algorithm: (trisomy 18 OR Edward* syndrome) AND hepatoblastoma. Using the Covidence software, two researchers (among I.A.Z., C.D.K., S.K.) screened the titles and abstracts initially and subsequently the full texts of the retrieved records. Any discrepancies were identified and resolved through quality control discussions. Reference lists and previously published reviews were hand-searched for potentially relevant, missed studies utilizing systematic snowball methodology [12].

2.3. Data tabulation and extraction

A standardized form was used for data tabulation and extraction from included studies for evidence synthesis. Two researchers (C.D.K., S.K.) tabulated and extracted the data independent of each other, and any potential discrepancies were identified and resolved with another author (I.A.Z.). The following study and demographic data were extracted for each eligible study: first author, year of publication, center and country, number of patients, patient age at diagnosis (in months), gestational age (in weeks), birth weight (in grams), sex, and mosaic status. Additionally, the following clinical data were extracted: presence of congenital heart defects and type, timing of diagnosis (incidental, symptom evaluation, surveillance, autopsy), tumor location (right, left, or both liver lobes) and number of nodules (single or multiple), PRE-Treatment EXTent of tumor (PRETEXT) stage, tumor size (in cm), alpha-fetoprotein (AFP) level at diagnosis (in ng/mL), tumor histology (fetal, embryonal, mixed fetal/embryonal), vascular invasion, and metastasis at diagnosis. Lastly, the following treatment and outcome variables were extracted: administration of chemotherapy, setting (neoadjuvant, adjuvant) and agents used, surgical treatment and type (wedge resection, segmentectomy, right or left hepatectomy or extended hepatectomy, liver transplantation), locoregional modalities (chemoembolization or microwave ablation), postoperative complications, disease recurrence, vital status at last follow-up (alive, dead), cause of death, and follow-up time (in months).

2.4. Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and categorical variables as frequency and percentage. Data on characteristics and outcomes of interest were tabulated and analyzed cumulatively, while all relative rates were estimated according to the availability of data for each variable based on the Cochrane Handbook recommendations [13]. The denominators vary for certain variables since not all studies reported on all variables of interest. The Kaplan–Meier method was used to estimate the 1-, 3-, and 5-year overall survival rates. Statistical analysis was conducted using Stata IC 16.0 (StataCorp LLC, College Station, Texas).

3. Results

3.1. Systematic review of the literature

The systematic literature review yielded a total of 88 records after removal of duplicate records, 38 of which were considered potentially eligible and thus sought for retrieval. After full-text review, 29 of these records were included along with another 21 records identified through the snowball method for a total of 50 included studies [7,9,14–61] (Fig. 1) reporting on 70 patients with T18 and hepatoblastoma (Table 1). The majority of articles were from Japan (n = 34), followed by USA (n = 13), Singapore (n = 1), Slovenia (n = 1), and United Kingdom (n = 1).

3.2. Cohort

The median patient age at diagnosis was 11.5 months (IQR: 7.0–21.0), the median gestational age was 37.0 weeks (35.0–40.0), the median birth weight was 1,630 g (IQR: 1,257–1,922), 85.9% were female (n = 55/64), and 15.0% had mosaic T18 (n = 6/40). The majority had congenital heart defects (89.7%, n = 52/58) and details

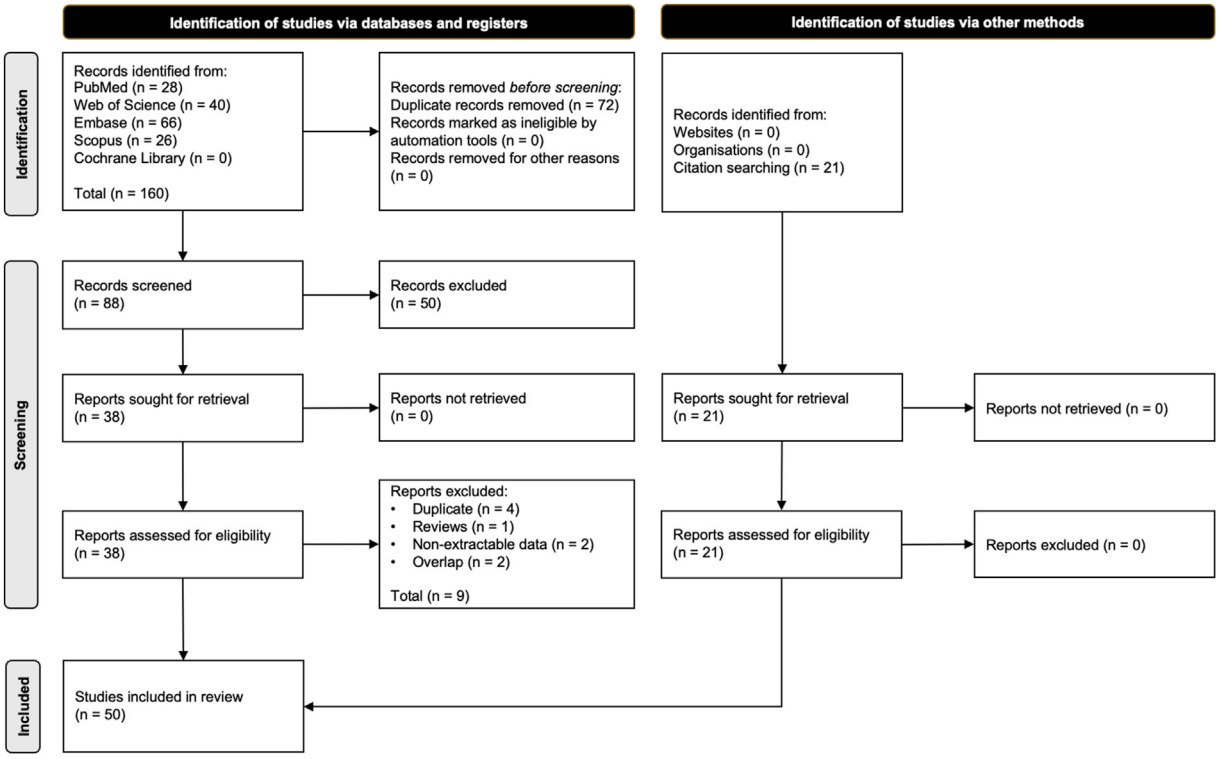

Fig. 1. PRISMA flow diagram.

on the specific diagnoses are provided in Table 2. The diagnosis of hepatoblastoma was made during symptom evaluation in 45.5% (n = 15/33), incidentally in 24.2% (n = 8/33), during surveillance with abdominal ultrasound in 18.2% (n = 6/33), and at autopsy in 12.1% (n = 4/33). Almost all symptomatic patients presented with hepatomegaly or abdominal mass (86.7%, n = 13/15), one with anemia (6.7%, n = 1/15), and one with esophageal reflux and fever (6.7%, n = 1/15). None of the patients had any additional reported malignancies (e.g., Wilms tumor).

Most tumors were in the right liver lobe (71.9%; n = 23/32) followed by both lobes in 15.6% (n = 5/32; two of which were large centrally located tumors) and less frequently in the left lobe (12.5%; n = 4/32), while 33.3% of the patients had multiple tumors (n = 14/42). The PRETEXT stage distribution was stage I in 27.6% (n = 8/29), stage II in 27.6% (n = 8/29), stage III in 24.1% (n = 7/29), and stage IV in 20.7% (n = 6/29). The median AFP level at diagnosis was 25,735.0 ng/mL (IQR: 2,410.0–98,220.0) and the median tumor size was 6.4 cm (IQR: 3.7–8.2). The histology was fetal in 76.2% (n = 32/42), embryonal in 2.4% (n = 1/42), and mixed fetal/embryonal in 21.4% (n = 9/42). Vascular invasion was seen in 7.1% (n = 1/14) and metastasis at diagnosis was present in 3.8% (n = 1/26). For the six patients diagnosed during abdominal ultrasound surveillance, the median tumor size was 4.3 cm (IQR: 3.0–6.3); five of them had PRETEXT stage I or II, while PRETEXT stage was not reported for the last one.

Neoadjuvant chemotherapy was administered in 42.6% (n = 26/61) with the most common chemotherapy agents used being cisplatin (CDDP) (25.5%, n = 14/55), doxorubicin (12.7%, n = 7/55), vincristine (10.9%, n = 6/55), 5-fluorouracil (5.5%, n = 3/55), irinotecan (5.5%, n = 3/55), etoposide (3.6%, n = 2/55), and carboplatin (1.8%, n = 1/55). There was significant heterogeneity in the regimen used with most patients receiving CDDP-based chemotherapy, five of whom received a CDDP/doxorubicin regimen (three CDDP/THP-ADR and two PLADO) and one received the C5V regimen (CDDP/5-fluorouracil/vincristine). Adjuvant chemotherapy was administered in 31.6% (n = 18/57) with the most common chemotherapy agents used being CDDP (23.5%, n = 12/51), doxorubicin (7.8%, n = 4/51), vincristine (5.9%, n = 3/51), 5-fluorouracil (5.9%, n = 3/51), and etoposide (2.0%, n = 1/51). Similarly, there was significant heterogeneity in the regimen used with most patients receiving CDDP-based chemotherapy, three of whom received a CDDP/doxorubicin regimen (two PLADO and one CDDP/THP-ADR), two received the C5V regimen, and one received both the C5V and PLADO regimens.

Surgical treatment was performed in 64.2% (n = 43/67). The specific procedure was reported for 21 patients and included right hepatectomy in 52.4% (n = 11/21), wedge resection in 28.6% (n = 6/21), right posterior segmentectomy in 9.5% (n = 2/21; one child also underwent caudate lobectomy), extended right hepatectomy in 4.8% (n = 1/21), and extended left hepatectomy in 4.8% (n = 1/21; also underwent chemoembolization after neoadjuvant chemotherapy and before surgery but ultimately required resection due to aberrant vascular anatomy). One of the patients who underwent wedge resection required a second wedge resection due to recurrence to the liver followed ultimately by whole graft deceased donor liver transplantation due to a second liver recurrence. One patient underwent only microwave ablation due to cardiac comorbidities and demonstrated complete tumor response. In the surgically treated patients, the immediate postoperative complications reported were infectious in four and ileus in two. The most common reasons for not pursuing surgery included the concomitant severe cardiopulmonary comorbidities, advanced hepatoblastoma stage, or the family's decision.

All patients with PRETEXT stage I underwent upfront resection with or without adjuvant chemotherapy, while patients with PRETEXT stage II received different modalities on a case-by-case basis among neoadjuvant chemotherapy, upfront resection, or locoregional treatment with or without adjuvant chemotherapy.

Table 1
Clinical and demographic data, management, and outcomes of children with T18 and hepatoblastoma.

Author, Year	Gender	Karyotype	CHD	Age at diagnosis (months)	Lobe	AFP at diagnosis (ng/mL)	PRETEXT stage	Histology	Tumor size at diagnosis (cm)	Treatment	Outcome (follow-up in months from diagnosis)	Cause of death
Abe, 1983 [14]	F	Full	PDA	9	NA	NA	NA	fetal	NA	No treatment	Dead (autopsy)	Heart failure
Dasouki, 1987 [15]	F	Full	VSD/PH	33	Both	NA	IV	NA	NA	No treatment	Dead (0.7)	Tumor progression
Mamlok, 1989 [16]	F	Full	VSD/ASD/BAV/PH	4	Right	NA	NA	embryonal	NA	No treatment	Dead (autopsy)	Heart failure
Ariwa, 1992 [17]	F	Full	VSD	10	NA	286,000	NA	fetal	NA	Chemotherapy → Surgery	Dead (10)	Tumor progression
Tanaka, 1992 [18]	F	Mosaic	VSD	24	Right	127,661	NA	fetal	NA	Surgery	Alive (33)	NA
Kuefer, 1995 [19]	F	Full	VSD	30	NA	NA	NA	NA	NA	No treatment	Dead (4)	Tumor progression
Bove, 1996 [20]	F	Full	PH	21	Right	6000	NA	mixed	9.0	Surgery	Dead (5)	Tumor progression
Teraguchi, 1997 [21]	F	Full	VSD/PDA/PH	6.5	Right	16,000	NA	fetal	NA	Surgery	Dead (53.5)	Influenza-associated encephalopathy
Hino, 1999 [22]	M	Full	VSD/ASD/PDA	10	NA	263,000	NA	fetal	NA	No treatment	Dead (3)	Unknown
Suzuki, 1999 [23]	F	Full	VSD	4	NA	1,130,000	NA	fetal	NA	Chemotherapy → Surgery	Alive (20)	NA
Kohn, 2000 [56]	F	Mosaic	None	16	Right	NA	NA	NA	NA	NA	NA	NA
Matsuoka, 2000 [24]	F	Full	VSD/ASD/PDA/DORV	4	NA	NA	NA	fetal	NA	No treatment	Dead (autopsy)	Unknown
Uemura, 2000 [25]	F	Full	VSD/ASD/PDA	5	NA	NA	NA	fetal	NA	No treatment	Dead (autopsy)	Respiratory failure
Maruyama, 2001 [26]	F	Full	VSD	3.4	Left	90,000	NA	fetal	1.5	No treatment	Dead (2.1)	Heart failure
Ito, 2004 [27]	F	Full	VSD	6	NA	NA	NA	NA	NA	Chemotherapy	NA	NA
Takahashi, 2004 [28]	F	Mosaic	VSD	9	NA	NA	NA	NA	NA	Chemotherapy	Alive (11)	NA
Nishi, 2006 [29]	F	Full	PH/DORV	12	NA	NA	NA	NA	NA	Chemotherapy	Dead (0.3)	Sudden death
Watanabe, 2006 [30]	F	Full	DORV	10	NA	NA	NA	NA	NA	Chemotherapy → Surgery planned	NA	NA
Ishibashi, 2009 [31]	F	Full	VSD/PDA	5	Right	384,789	NA	fetal	NA	Surgery	Alive (6)	NA
Kitanovski, 2009 [32]	F	Full	None	6	Both	51,542	NA	fetal	9.6	No treatment	Dead (1)	Tumor progression
Kunikata, 2009 [33]	NA	Full	VSD/PDA	6	NA	NA	NA	NA	NA	Chemotherapy	Dead (1)	Tumor progression
Fernandez, 2011 [34]	M	Mosaic	None	9	Right	345	I	fetal	4.3	Surgery → Chemotherapy → Surgery → Chemotherapy → Liver transplantation → Chemotherapy	Alive (28 after liver transplantation)	NA
Ohashi, 2012 [35]	F	Full	VSD/PDA	9	NA	NA	NA	NA	NA	No treatment	Dead (1)	Pulmonary hypertension
Pereira, 2012 [36]	F	Mosaic	None	120	Left	1040	NA	fetal	13.0	Chemotherapy → Surgery	Alive (27 from surgery)	NA
Sugitate, 2012 [37]	F	Full	ASD/PDA	24	NA	NA	NA	NA	NA	Surgery	Dead (7)	Unknown
Uekusa, 2012 [38]	M	NA	Aortic coarctation	14	Right	141,900	III	fetal	11.7	Chemotherapy → Surgery → Chemotherapy	Alive (18)	NA
Hamamoto, 2013 [39]	F	NA	NA	19	NA	NA	NA	NA	NA	Chemotherapy → Surgery → Chemotherapy	Alive (NA)	NA
Onitake, 2013 [40]	F	NA	VSD/PDA	12	NA	NA	NA	NA	NA	Chemotherapy → Surgery → Chemotherapy	Alive (15)	NA
Kobayashi, 2014 [41]	F	NA	VSD/PDA	19	NA	NA	NA	NA	NA	Surgery → Chemotherapy	Alive (5)	NA
Takagi, 2014 [42]	F	Full	NA	6	NA	NA	NA	NA	NA	Surgery	Alive (3)	NA
Tan, 2014 [43]	F	Full	VSD/ASD/PDA	12	Right	8563	I	fetal	6.3	Surgery	Alive (17)	NA
	F	Full	VSD/ASD/PDA	7	Right	7856	I	mixed	5.3	Surgery	Dead (7)	Cardiopulmonary collapse
Yada, 2014 [44]	F	NA	NA	NA	Right	NA	II	fetal	NA	Surgery	Alive (67)	NA
Tamaichi, 2015 [45]	F	NA	VSD	60	NA	NA	NA	NA	NA	Chemotherapy	Dead (1)	Pulmonary hypertension
Valentin, 2015 [46]	F	Full	NA	12	Right	57.1	II	fetal	NA	Surgery → Chemotherapy	Alive (NA)	NA
	F	Full	CHD, not specified	11	NA	9160	NA	fetal	NA	NA	Dead (NA)	Cardiac complications
	F	Full	NA	48	NA	841	NA	fetal	NA	Surgery	Alive (120)	NA
Ahmad, 2016 [47]	M	Mosaic	VSD/PDA	18	Right	2259	II	mixed	6.5	Chemotherapy → Surgery → Chemotherapy → Surgery	Alive (44 from end of treatment)	NA
Libuchi, 2016 [48]	F	NA	VSD/PH	8	NA	NA	NA	NA	NA	No treatment	Dead (0)	Tumor progression
Maeda, 2016 [49]	F	NA	VSD	7	NA	NA	NA	NA	NA	No treatment	Dead (2)	Tumor lysis syndrome
Miyagawa, 2016 [50]	F	NA	VSD	9	NA	NA	NA	NA	NA	Chemotherapy → Surgery → Chemotherapy	Alive (2)	NA
Inoue, 2018 [51]	F	NA	VSD/PDA	12	Right	33	I	mixed	1.5	Surgery → Chemotherapy	Alive (39.4)	NA
	F	NA	VSD/ASD/PDA	10	Both	7275	IV	mixed	3.0	Chemotherapy	Alive (24.8)	NA

	F	NA	VSD/PDA	18	Right	501	I	mixed	3.0	Surgery → Chemotherapy	Alive (12)	NA
	M	NA	VSD/PDA	22	Right	98,220	II	fetal	10.0	Chemotherapy → Surgery → Chemotherapy	Alive (7.2)	NA
Tanaka, 2018 [52]	M	NA	CHD, not specified	36	NA	NA	NA	NA	NA	No treatment	Dead (5)	Hemorrhagic shock due to intra-tumoral bleeding
Farmakis, 2019 [7]	F	Full	NA	21	NA	2410	IV	fetal	NA	Chemotherapy → Surgery	Alive (36)	NA
Hesh, 2019 [53]	F	NA	VSD/PDA/BAV/PH	14	Right	85	II	fetal	3.1	Microwave ablation	Alive (9)	NA
Lucas, 2019 [54]	F	NA	PDA/BAV/PH	7	Right	28,000	I	mixed	3.7	Surgery → Chemotherapy	Alive (9 off therapy)	NA
	F	NA	VSD/PDA/PH	9	Left	88,265	II	fetal	5.0	Chemotherapy → Chemoembolization → Surgery → Chemotherapy	Alive (1.5 from surgery)	NA
Ashina, 2020 [55]	F	NA	VSD	24	NA	133,925	III	mixed	NA	Chemotherapy → Surgery	NA	NA
Murase, 2020 [57]	F	Full	VSD/PDA/PAPVC	24	Right	29,172	II	fetal	8.0	Surgery	Alive (169)	NA
	F	Full	VSD/PH	12	Right	162,000	I	fetal	8.0	Surgery	Dead (10)	Severe pulmonary hypertension
	F	Full	VSD/PDA	27	Right	25,735	I	mixed	5.5	Surgery → Chemotherapy	Alive (45)	NA
	F	Full	VSD/PDA	9	Both	30,947	IV	NA	7.2	Chemotherapy → Surgery → Chemotherapy	Alive (25)	NA
	F	Full	PDA/PA/DORV	32	Right	19,630	II	NA	8.2	No treatment	Dead (15)	Aspiration pneumonia
Irikura, 2022 [58]	NA	NA	VSD	NA	NA	NA	IV	NA	NA	Chemotherapy → Surgery	Alive (25)	NA
	NA	NA	DORV	NA	NA	NA	IV	NA	NA	Chemotherapy → Surgery	Dead (0.2 from surgery)	Sudden death
	NA	NA	CHD, not specified	NA	NA	NA	III	NA	NA	Chemotherapy	Dead (13)	Tumor progression
	NA	NA	CHD, not specified	NA	NA	NA	III	NA	NA	Chemotherapy	Alive (12)	NA
	NA	NA	VSD	NA	NA	NA	III	NA	NA	Chemotherapy	Alive (1)	NA
Honda 2023 [59]	M	NA	VSD	15	Both	NA	III	NA	NA	Chemotherapy → Surgery → Chemotherapy	Alive (19)	NA
Schepers 2023 [9]	F	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
	F	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
	F	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
	F	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
	F	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
	M	NA	NA	NA	NA	NA	NA	fetal	NA	Surgery	Alive	NA
Garg 2024 [60]	F	Full	VSD/ASD/PDA/PFO/ polyvalvular dysplasia	6	Left	NA	NA	fetal	NA	Surgery → Chemotherapy	Alive (22 from surgery)	NA
Shirane 2024 [61]	M	Full	VSD/PDA/PH/ polyvalvular dysplasia	10	Right	46,350	III	NA	6.9	Chemotherapy → Surgery → Chemotherapy	Alive (44 from surgery)	NA

AFP = alpha fetoprotein; ASD = atrial septal defect; BAV = bicuspid aortic valve; CHD = congenital heart defect; DORV = double outlet right ventricle; NA = not available; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PA = pulmonary atresia; PAPVC = Partial anomalous pulmonary venous connection; PH = pulmonary hypertension; PRETEXT = PRE-Treatment EXTent of tumor; VSD = ventricular septal defect.

Table 2
Concomitant cardiac comorbidities.

Comorbidity	Percentage	n with comorbidity/Total n with available data
VSD	75.9%	n = 41/54
PDA	50.9%	n = 27/53
Pulmonary hypertension	21.6%	n = 11/51
ASD	17.0%	n = 9/53
Double outlet right ventricle	9.6%	n = 5/52
Congenital heart defect, not specified	8.8%	n = 5/57
Bicuspid aortic valve	6.0%	n = 3/50
Polyvalvular dysplasia	3.8%	n = 2/52
Aortic coarctation	2.0%	n = 1/51
Pulmonary atresia	1.9%	n = 1/52
Partial anomalous pulmonary venous connection	1.9%	n = 1/52
Patent foramen ovale	1.9%	n = 1/52

ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

Except for a patient who experienced rapid deterioration, all patients with PRETEXT stage III or IV underwent neoadjuvant chemotherapy followed by resection when possible, depending on the tumor stage and cardiopulmonary status of the patient. Using data from the available studies, we propose the algorithm shown in Fig. 2 for the management of hepatoblastoma in children with T18, which should be considered in conjunction with the guidelines and recommendations of the Children's Oncology Group on the management of hepatoblastoma.

The four children diagnosed with hepatoblastoma on autopsy were 3, 4, 5, and 9 months old, respectively. Of the remaining 66 patients, survival status was available for 62 and overall mortality was 35.5% (n = 22/62) over a median follow-up of 11.0 months (IQR: 4.0–25.0). Fifty-three of these patients had complete data for Kaplan–Meier estimation, and the median overall survival was 53.5 months, while the 1-, 3-, and 5-year overall survival rates were 63.9%, 58.2%, and 43.7%, respectively (Fig. 3). Among the six patients with mosaic T18, one had no survival data available, but the remaining five were alive over a median follow-up of 33.0 months (IQR: 27.0–36.5). Among the 26 deceased patients (including those diagnosed on autopsy), the causes of death were cardiopulmonary disease (38.5%, n = 10/26), tumor progression (30.8%, n = 8/26), sudden death (7.7%, n = 2/26), tumor lysis syndrome (3.8%, n = 1/26), hemorrhagic shock due to intra-tumoral bleeding (3.8%, n = 1/26), influenza-associated encephalopathy (3.8%, n = 1/26), or unknown (11.5%, n = 3/26). Three surgically treated patients experienced disease recurrence within 1 month (initial tumor at right lobe but recurred to left lobe), 1.5 months (widespread bone metastases), and 21 months (initial tumor at right lobe but recurred to left lobe), respectively; one of them received liver transplantation and remained disease-free 36.5 months from diagnosis, one died due to influenza-associated encephalopathy 53.5 months from diagnosis, and one died due to tumor progression (bone metastases) 5 months from diagnosis.

4. Discussion

The present systematic literature review reports on 70 children with T18 and hepatoblastoma and shows that T18 does not preclude resection with curative intent for hepatoblastoma. After diagnosis and staging of hepatoblastoma, a goals of care discussion should take place and the different treatment modalities need to be discussed with the family contemplating the patient's underlying physiologic state, cardiopulmonary comorbidities, tumor staging, and the family's overall goals. These data suggest that most children with T18 are often diagnosed with hepatoblastoma in infancy during evaluation of symptoms and the majority have concomitant congenital heart defects or pulmonary hypertension. Nevertheless, more than 60% of the patients underwent surgical treatment, while the most common reasons for not pursuing surgery were the concomitant severe cardiopulmonary comorbidities or the family's decision.

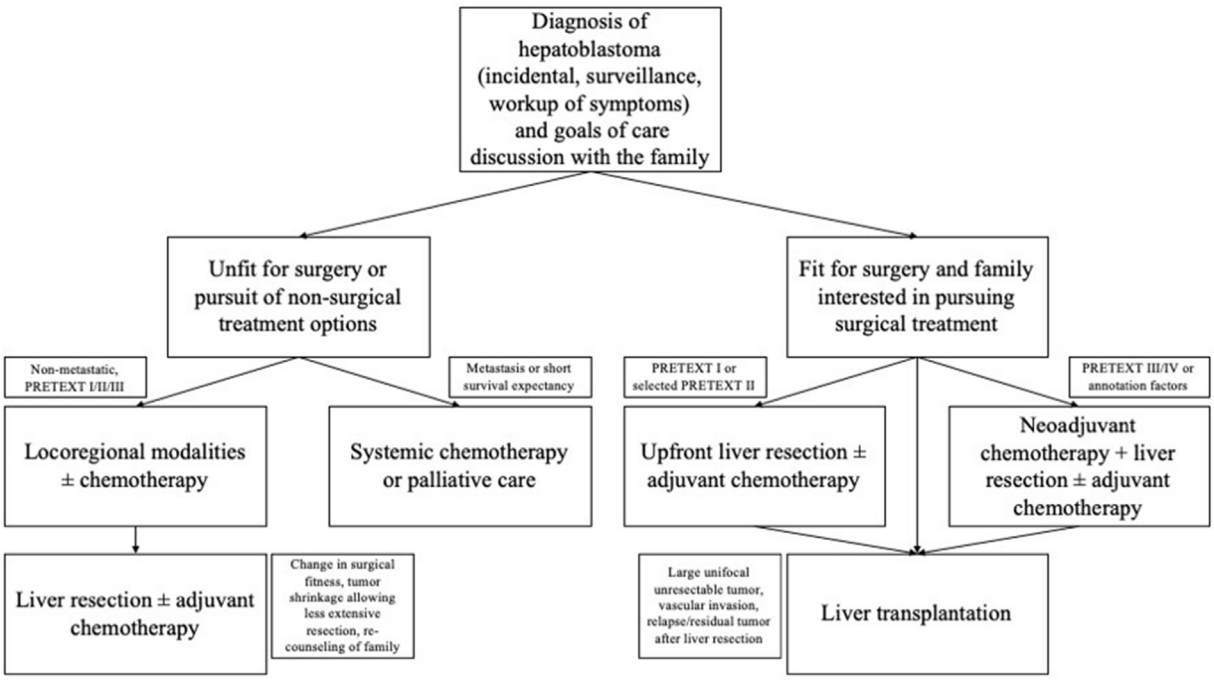

Fig. 2. Proposed treatment algorithm for hepatoblastoma in T18.

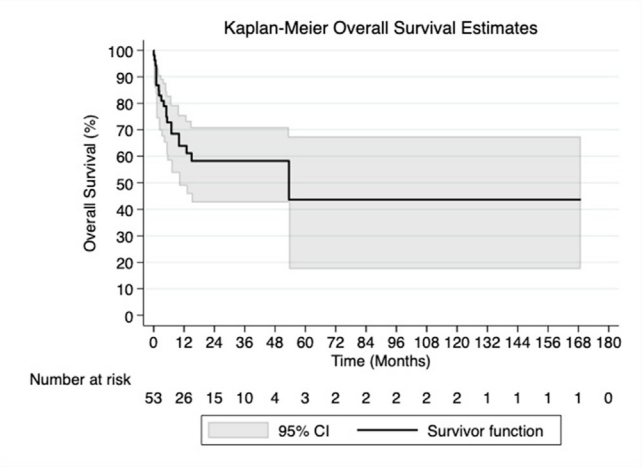

Fig. 3. Kaplan–Meier overall survival curve.

In a recent US cancer registry analysis of children with hepatoblastoma, it was found that the median age at diagnosis was 1 year, the median tumor size was 10 cm, 46.9% had a solitary tumor, 27.2% had vascular invasion, and 21.4% had metastasis at diagnosis [62]. Additionally, 77.3% underwent surgical treatment and 95.1% received chemotherapy [62]. The age at time of diagnosis appears to be consistent in hepatoblastoma with or without T18. Although in our T18 cohort a higher proportion of children had solitary (66.7%) and smaller hepatoblastomas (median size 6.4 cm) with lower rates of vascular invasion (7.1%) and metastasis (3.8%), the proportion of T18 children undergoing surgical treatment (64.2%) and chemotherapy (42.6% neoadjuvant and 31.6% adjuvant) was lower than those without T18 [62]. Moreover, the 5-year overall survival rate for hepatoblastoma in the setting of T18 was found to be 43.7% when compared with 76.6% in allcomers [62]. Notably, recent evidence has also identified the presence of disparities in the surgical management of hepatoblastoma in children [63].

In this pooled analysis, 15.0% of the patients had mosaic T18, in which two different cell lines exist in the same person with one cell line comprised of two copies of chromosome 18 and the other one comprised of three copies [64]. Patients with mosaic T18 are considered to have significant phenotypical variation and in most scenarios exhibit a less severe phenotype associated with longer life expectancy [7]. There is a hypothesis suggesting the potentially protective role of the lack of T18 cells within the tumor, while data also suggest that the presence of a third dose of the thymidylate synthetase gene, located on chromosome 18, could be associated with resistance to chemotherapy [34,36]. Indeed, in this review, patients with mosaic T18 and hepatoblastoma exhibited favorable long-term survival with multimodal treatment including surgery and/or chemotherapy with all five patients with available data being alive over a median follow-up of 33 months [18,28,34,36,47].

Several studies have tried to provide solid tumor screening recommendations for T18. The major challenge is that the high mortality during infancy may lead to underestimation of the true solid tumor incidence in patients with T18. It is possible that if more autopsies were performed in this population, more hepatoblastomas may have actually been identified [14,16,24,25]. In addition to the difficulty estimating the incidence of hepatoblastoma in T18, the concept of solid tumor screening in this population is also controversial due to potential refusal of further workup or invasive procedures by the family. Provided that screening aligns with the family's goals of care and there is adequate estimated life expectancy, current recommendations include baseline serum AFP level at birth and repeated every three months until four years of age along with complete abdominal ultrasound every three months until four years of age, and then only renal ultrasound until age seven years because of the persistent risk of developing Wilms tumor [7]. These recommendations for obtaining ultrasounds every three months are derived from the current screening recommendations in place for patients with Beckwith-Wiedemann syndrome [65]. The findings from our systematic review indicate that with these screening recommendations, all but two patients would have been diagnosed by the age of four years if not sooner, yet less than one-fifth of the patients were diagnosed during surveillance. Children with T18 diagnosed with hepatoblastoma during abdominal ultrasound surveillance in our study had PRETEXT stage I or II and the median tumor size was smaller (median 4.3 cm vs 6.4 cm in the entire cohort). Therefore, we believe that broader adoption of these screening recommendations may lead to earlier diagnosis of hepatoblastoma in patients with T18, which may allow for earlier treatment with curative intent and improved outcomes.

To our knowledge, this is the first systematic literature review to describe the presentation, management, and outcomes of patients with T18 and hepatoblastoma. Nonetheless, our study has certain limitations. Despite our systematic literature search, only small case series or case reports were found due to the rarity of hepatoblastoma in patients with T18, and thus impart a degree of inherent selection and publication bias. Additionally, the findings of this review are characterized by increased heterogeneity since family decisions and patient management may differ based on country and year of presentation. Finally, as with any systematic review, some of the articles did not report on all variables of interest, and thus all relative rates were calculated based on data availability.

In conclusion, T18 does not preclude resection with curative intent for hepatoblastoma if aligned with the family's goals and wishes. Combination of surgery and chemotherapy should be considered in children with T18 and hepatoblastoma on an individualized basis depending on tumor characteristics and underlying cardiopulmonary comorbidities. Locoregional modalities may have a role in the setting of severe cardiopulmonary comorbidities.

Previous communication

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Conflicts of interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2024.06.005.

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