Clinical presentation of childhood soft tissue sarcomas: a systematic review and meta-analysis

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ABSTRACT

Background Time to diagnosis (TTD) of childhood soft tissue sarcoma (STS) is significantly associated with survival. This review aims to identify pre-diagnostic symptoms/signs to inform earlier diagnosis interventions.

Methods Medline, Embase, Cochrane and Web-of-Science were searched between January 2010 and February 2021 for studies including children (<18 years) diagnosed with STS, with no language restrictions. Pooled proportions of symptoms/signs were calculated and subanalysed by tumour location and age.

Results Fifty-nine eligible studies were identified, totalling 2462 cases. The most frequent symptoms were lump/swelling (38%, 95% CI 27% to 51%), pain (6%, 95% CI 3% to 10%), cutaneous changes (4%, 95% CI 0 to 9%), localised eye swelling (3%, 95% CI 0 to 7%), cranial nerve deficits (2%, 95% CI 0 to 5%) and constitutional symptoms (2%, 95% CI 0 to 5%). Symptoms varied by location and age. Localised eye swelling (20%, 95% CI 3% to 45%), cranial nerve deficits (14%, 95% CI 4% to 28%) and impaired visual function (6%, 95% CI 0 to 17%) were frequent in head and neck tumours. For abdomen/pelvic tumours, urinary symptoms (24%, 95% CI 5% to 15%), abdominal distension/discomfort (22%, 95% CI 4% to 47%), genital lump/swelling (16%, 95% CI 1% to 42%), constitutional symptoms (9%, 95% CI 0%] to 23%), vaginal bleeding (7%, 95%C I 0 to 21%) and bowel habit changes (6%, 95% CI 0 to 17%) were frequent. In <5 years, consumptive coagulopathy (16%, 95% CI 0 to 48%), cutaneous changes (5%, 95% CI 0 to 40%), genital lump/swelling (4%, 95% CI 0 to 14%), reduced mobility (3%, 95% CI 0 to 11%), vaginal bleeding (2%, 95% CI 0 to 11%) and bleeding/bruising/petechiae (2%, 95% CI 0 to 20%) were frequent compared with lump/swelling, constitutional symptoms, pain and headaches which were frequent among >11 years.

Conclusions For STS, pre-diagnostic symptoms differ by age and location, highlighting the need to tailor early diagnosis interventions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Childhood soft tissue sarcomas (STS) present with a non-specific lump/swelling and other non-specified compressive symptoms and/or signs, which have not been fully explored in the literature.
⇒ Time to diagnosis (TTD) of STS is significantly associated with children's survival outcomes and contribute to disease-related morbidity.
⇒ A more detailed understanding of clinical presentation is needed in order to accelerate diagnosis and improve outcomes.

WHAT THIS STUDY ADDS

⇒ This is the first systematic review and meta-analysis including all currently available evidence.
⇒ It is the largest sample of children diagnosed with any STS subtype, in any tumour location, making the findings widely applicable across different clinical contexts.
⇒ This study identifies that pre-diagnostic symptoms in childhood STS are location-related and vary according to age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data will be used to produce evidence-based guidelines for clinicians and awareness tools for the public to aid prompt recognition of these signs/symptoms.

INTRODUCTION

Childhood cancer affects 400 000 children worldwide each year.[1] Around 1838 children are diagnosed with cancer annually in the UK, 154 of these are soft tissue sarcomas (STS).[2 3] STS encompasses a heterogeneous group of malignant solid tumours, including rhabdomyosarcomas, peripheral nerve sheath tumours and fibrosarcomas.

The overall 5-year survival can vary from 35% to 96%, depending on tumour size, stage and metastasis at diagnosis.[4] The optimal survival rates observed in clinical trials are not widely applicable to all, which is invariably influenced by access to healthcare and effective treatment. There is a notably unfavourable outcome for ages <5 years and >10 years.[5 6]

STS has the second longest time to diagnosis (TTD) of all childhood cancers.[7] Importantly, TTD of STS has an independent, significant association with overall survival.[8] A longer TTD also contributes to more advanced disease, necessitating more intensive treatment, in the form of additional radiotherapy, limb removal and/or substantial deformity. Reducing unnecessary delays has the potential to substantially reduce mortality and treatment-related morbidity.

A crucial modifiable factor contributing to TTD in STS is the limited literature outlining its clinical presentation prior to diagnosis. The limited evidence base acts as a barrier to early recognition and the development of interventions to promote

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earlier diagnosis. Previously published literature states that STS presents with a non-specified lump/swelling in various locations and/or location-specific compression symptoms.[9–11] Further interpretation into clinical presentation is limited by small sample sizes, focusing on subsets of certain locations or subtypes and the rarity of this tumour.[12–15]

In other childhood cancers, clinical presentation varies according to tumour location.[16] The location of STS differs significantly according to age.[5 17] There is a larger proportion of head/neck or intra-abdominal STS in those aged <10 years and a relative tendency for extremity or trunk STS in those aged >10 years.[17] Similar to how the physiological growth rate of certain tissues strongly correlates with patterns of age-related incidence for other childhood cancers,[18 19] it is plausible that this relationship between age and STS location reflects an age-determined variation in the physiological growth rates of soft tissues in different anatomical locations.

The aim of this study is to provide a detailed, clinically relevant overview of the symptoms and/or signs in children diagnosed with STS and explore if these vary according to location and age of diagnosis.

METHODS

Search strategy and inclusion criteria

This review was conducted in alignment with Preferred Reporting Items for Systematic reviews and Meta-Analysis[20] and Strengthening the Reporting of Observational Studies in Epidemiology guidance.[21]

Our search strategy included keywords; 'soft tissue sarcoma(s)', 'rhabdomyosarcoma', 'non-rhabdomyosarcoma'; and, 'child', 'infan(t)', 'adolescen(t)', 'p(a)ediatric(s)'; and 'diagnosis', 'symptom(s)', 'signs and symptoms', 'clinical presentation(s)', 'clinical feature(s)', or 'physical examination(s)'. Medline (OVID), Embase (OVID), Web of Science and Cochrane were searched, from January 2010 to February 2021, with no language restrictions. All cross-sectional studies and case series, including >10 paediatric cases (diagnosed <18 years of age) with sufficient information about clinical presentation, symptoms/signs, were included. Cases included are defined by International Classification of Childhood Cancer (ICCC) Recode International Classification of Diseases for Oncology (ICD-O-3)/WHO 2008 definition of childhood STS, (online supplemental table S1).[22] Case reports or letters to the editor were excluded.

After removal of duplicate records, screening of titles, abstracts and full texts was conducted by an independent researcher (LNC) and agreed with two other researchers (J-FL, DS). A comprehensive approach to identify all eligible grey literature was adopted, including searching reference lists and contacting authors.

Data extraction

Data were extracted by an independent researcher (LNC), using a standard proforma, quality was checked by others (J-FL, DS). Data items collected included study characteristics, year of publication, country, recruitment period, number of patients, study design, data source, tumour location and age. Symptom presentation was recorded as reported. If the presence of a symptom/sign could not be ascertained, it was assumed to be absent. When it was not possible to separate symptoms reported in combination, they were extracted as a cluster of symptoms.

Quality assessment

The quality of eligible studies was comprehensively assessed by evaluating the following methodological domains; recruitment period, number of institutions, sample selection, case ascertainment, data ascertainment and quality of reporting (online supplemental table S2).

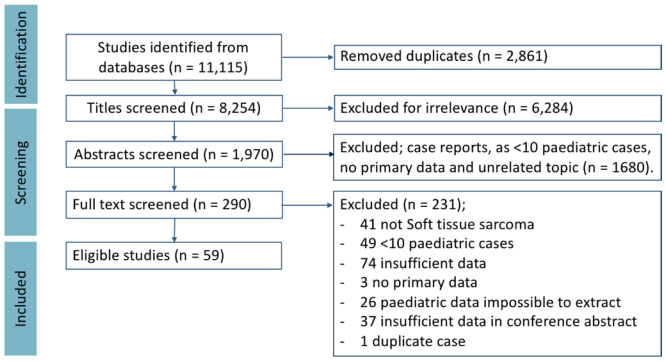

Figure 1 Flowchart of screening process to identify eligible studies.

Data analysis

Using STATA V.16.0 (StataCorp (2019). Stata Statistical Software: Release 16. College Station, Texas, USA; StataCorp LLC), the pooled proportion of symptoms/signs was calculated by calculating the proportion of each symptom/sign within each individual study, as weighted according to its variance, then calculating the sum of proportions. The total proportion was divided by the sum of weights to give a pooled proportion. Most analyses showed considerable heterogeneity (I^2>75%), therefore a random effect model was used, and Freeman-Tukey double arcsine transformation of proportions was also incorporated.

A predetermined threshold for symptoms/signs reported in 2% or more of the cohort was set, as a practical compromise between identifying clinically relevant symptoms and minimising the potential risk of overinterpreting non-specific symptoms.

Subanalyses according to tumour location and age were conducted.

RESULTS

A total of 11 112 studies were identified. After removal of duplicates, 8254 studies remained. Screening of titles, abstracts and full texts identified 59 eligible studies (figure 1), including 2462 cases of childhood STS, across 32 countries (table 1). The quality was comprehensively evaluated and summarised (online supplemental table S3). A total of 101 symptoms/signs were reported. Overlapping clinical features were clustered together into 43 symptoms and signs. Symptoms/signs were recorded as either pre-diagnostic or present at diagnosis in 44 studies, while 15 studies did not specify when the symptoms/signs were identified.

Overall, the most common symptoms/signs were lump/swelling (38%), pain (6%), cutaneous changes (4%), localised eye swelling (3%), constitutional symptoms (2%), abnormal full blood count (2%) and cranial nerve deficits (2%) (figure 2).

Thirty-two out of 44 studies (n=1824) reported symptoms in all locations.[8 23–53] Further analysis restricted to these studies showed similar results. The most common symptoms/signs were lump/swelling (68%), pain (7%), cutaneous changes (9%), constitutional symptoms (2%) and abnormal full blood count (2%).

Tumour location

Symptoms/signs were analysed according to tumour location; 17 studies reported symptoms for head and neck (H&N) STS[54–70]; 9 studies reported symptoms in abdomen and/or pelvis (A&P)

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Table 1 Characteristics of all studies

Authors	Country	Study recruitment period	N	Study design	Source of data (primary or secondary/ tertiary care records)	Number of institutions	Tumour location	Age, mean (years)	Age, median (years)	Age, range (years)
Abdel Wahab *et al*[23]	France	1995–2008	15	O	MR (NS)	1	All	13	13	3–18
An *et al*[24]	Korea	2007–2016	11	O	MR (S/T)	1	All	9.5	12.8	0.25–15.8
Benesch *et al*[54]	German, Austria, Switzerland	1988–2009	19	O	MR (NS)	>1*	H&N	8.4	9.7	0.5–7.8
Bots *et al*[25]	Hungary	2000–2016	90	O	MR (S/T)	1	All	8.6	7.1	0.28–18
Bottcher *et al*[55]	Germany	1996–2016	28	O	MR (S/T)	1	H&N	6.8	–	0–18
Boutroux *et al*[56]	France	1975–2010	95	O	MR (S/T)	1	H&N	–	6	0.7–19.5
Bravo-Ljubetic *et al*[57]	Spain	1982–2011	14	O	MR (S/T)	1	H&N	–	8	0.25–12.8
Cai *et al*[26]	China	1998–2013	51	O	MR (S/T)	1	All	5	5	0.1–13.5
Cox *et al*[27]	Malawi	2003–2009	81	O	MR (S/T)	2	All	–	8	1.9–16.9
Croteau *et al*[28]	USA	1991–2009	105	O	MR (S/T)	1	All	–	0.16	0–18
de Carvalho *et al*[58]	Brazil	2007–2016	14	Cross-sectional analysis of cohort study	MR (NS)	12	H&N	–	14	3–18
Dehner *et al*[71]	USA	1990–2010	12	O	MR (S/T)	3	P	9.6	10.5	0.75–15
Demir *et al*[29]	Turkey	1988–2009	13	O	MR (NS)	1	All	–	11	0.16–18
Deyrup *et al*[30]	USA	Not specified	10	O	MR (S/T)	2	All	6.9	7	0.1–15
Diaconescu *et al*[31]	Romania	2000–2010	25	O	MR (S/T)	1	All	–	6.7	3 days-17
Dombrowski *et al*[59]	USA	1970–2015	97	O	MR (S/T)	1	H&N	–	5.8	0–18
El-Mallawany *et al*[32]	Malawi	2010–2013	70	O	MR (S/T)	1	All	–	8.6	1.7–17.9
El-Nadi *et al*[60]	Egypt	2007–2012	17	O	MR (S/T)	1	H&N	5.5	5.04	0.3–14.7
Fasina[61]	Nigeria	Not specified	22	O	NS (NS)	1	H&N	–	7	5–13
Fernandez-Pineda *et al*[72]	USA	1970–2009	13	O	MR (S/T)	1	P	–	3.7	0.16–15
Ferrari *et al*[8]	Italy	1977–2005	575	O	MR (S/T)	1	All	–	13	0–21
Fortunati *et al*[33]	Argentina	2002–2017	16	O	NS	1	All	–	11.5	0.25–16
Giuseppucci *et al*[80]	Argentina	1990–2014	13	O	MR (NS)	1	C	7.3	–	0.9–16.6
Häußler *et al*[62]	Germany	1996–2016	28	O	National Cancer Registry and MR (S/T)	1	H&N	6.8	–	0.1–16
Hemida *et al*[73]	Egypt	2007–2011	10	O	MR (S/T)	1	P	4.3	–	2–12
Hessissen *et al*[34]	Morocco	1995–2004	100	O	MR (S/T)	1	All	–	5	0.5–16
Hu and Zhou[35]	China	2011–2016	25	O	MR (S/T)	1	All	–	0.33	19 days–9
Hu *et al*[74]	China	2006–2018	30	O	MR (NS)	1	A&P	–	4.3	0.8–13
Ibikunle *et al*[63]	Nigeria	2013–2017	18	O	MR (S/T)	1	H&N	–	–	2–20
Iqbal *et al*[36]	USA	1980–2010	15	O	MR (S/T)	2	All	11.9	14	2–18
Ji *et al*[37]	China	2006–2018	28	O	Multicentre database and MR (S/T)	6	All	–	0.6	0–13
Kadhim *et al*[75]	USA	2000–2013	10	O	Cancer Registry and MR (NS)	1	P	–	–	0.7–2.1
Karamercan *et al*[38]	Turkey	1995–2018	30	NS	MR (NS)	1	All	8.3	–	0.13–16
Koo *et al*[39]	UK	2012–2015	21	Cross-sectional analysis of cohort study	Self-reported by patients via structured interviews 6 months after diagnosis	96	All	–	–	12–18
Lim *et al*[76]	UK	1994–2014	12	O	MR (NS)	(>1*)	P	6	–	1–15
Livio *et al*[64]	Argentina	1991–2011	22	O	MR (NS)	1	H&N	–	7.4	1.1–14.5
Maher *et al*[65]	USA	1990–2015	11	O	MR (S/T)	1	H&N	–	5	7 days–18
Mathey *et al*[40]	Argentina	2002–2017	42	O	MR (NS)	1	All	–	0.48	18 days–1
Missaoui *et al*[41]	Tunisia	1993–2007	30	O	MR (NS)	(>1*)	All	–	5.9	0.42–15
Okumu *et al*[66]	Kenya	2008–2008	13	O	MR (NS)	2	H&N	–	–	0–15

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Table 1 Continued

Authors	Country	Study recruitment period	N	Study design	Source of data (primary or secondary/ tertiary care records)	Number of institutions	Tumour location	Age, mean (years)	Age, median (years)	Age, range (years)
Papillard-Marechal *et al*[42]	France	2007–2011	71	O	MR (NS)	1	All	–	8.6	0–17.5
Parida *et al*[43]	USA	1980–2009	15	O	MR (S/T)	1	All	–	0.25	3 days–3
Perruccio *et al*[77]	Italy	1979–2004	10	Analysis of prospective trials	Multicentre database and MR (NS)	>1*	A	–	3	0.02–11
Pinheiro *et al*[44]	Portugal	2003–2013	51	O	NS	NS	All	–	10	<18
Posso-De Los Rios *et al*[45]	Canada	2002–2012	17	O	MR (S/T)	1	All	7.9	–	0–18
Reilly *et al*[67]	USA	1996–2014	17	O	MR (S/T)	1	H	–	6.3	0.67–19
Rifi *et al*[46]	Tunisia	1990–2007	68	O	MR (NS)	NS	All	9	–	<18
Ronghe *et al*[47]	Scotland	2001–2010	31	O	MR (NS)	1	All	–	4	0–18
Sachedina *et al*[78]	Australia	1996–2016	17	O	MR (S/T)	1	P	5.06	–	0–15
Shi *et al*[79]	China	2008–2015	12	O	MR (S/T)	1	A	5.47	–	1.7–15
Siwillis *et al*[48]	Tanzania	2011–2016	89	O	MR (S/T)	1	All	–	6	0.1–17
Stefan *et al*[49]	South Africa	1998–2009	70	O	MR (S/T)	3	All	–	6	0.8–13.6
Tsai *et al*[50]	Taiwan	1986–2011	13	O	MR (S/T)	1	All	–	15	0–18
Valdivielso-Ramos *et al*[51]	Spain	2000–2011	13	O	Multicentre database and MR (S/T)	20	All	–	15	0.3–17
Varan *et al*[52]	Turkey	1975–2013	10	O	MR (S.T)	1	All	–	8	1.5–18
Wang *et al*[68]	China	1995–2013	10	O	Patient/family reported via interviews and MR (NS)	1	H&N	8.1	6.5	3–16
Zhang *et al*[69]	China	2004–2010	39	O	MR (S/T)	1	H&N	–	6	0.25–14
Zhao *et al*[53]	China	1998–2008	23	O	MR (S/T)	1	All	5	–	0.6–12
Zorzi *et al*[70]	Canada	1985–2010	35	O	MR (N/S)	1	H&N	–	5.8	1–17.9

*Multicentre but number not specified.
All, all tumour locations (years); A&P, abdomen and pelvis; H&N, head and neck; MR, medical records; NS, not specified; O, observational; S/T, secondary or tertiary care medical records.

STS[71–79]; and only 1 study reported symptoms in patients with intrathoracic/chest STS.[80]

Head and neck

Seventeen studies (n=499) reported patients with STS located in the H&N. The most common symptoms/signs were localised eye swelling (20%), lump/swelling (16%),cranial nerve deficit (14%) and impaired visual function (6%) (figure 3A).

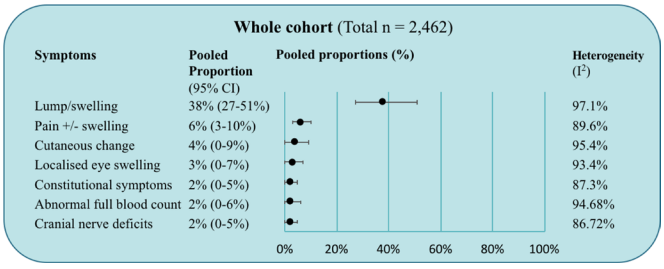

Figure 2 Pooled proportions for the most common pre-diagnostic symptoms/signs reported in the whole cohort.

Abdomen and pelvis

Nine studies (n=126) reported patients with STS located in the A&P. The most common symptoms/signs were urinary symptoms (24%), abdominal distension/discomfort (22%), genital mass/swelling (16%), pain (11%), constitutional symptoms (9%), lump/swelling (9%), vaginal bleeding or bloody discharge (7%), change in bowel habit (6%), obstructive jaundice (2%) and abnormal full blood count (2%) (figure 3B).

Chest

As only one study (n=13) reported patients with STS located in the chest/intrathoracic region, subanalysis was not conducted. Symptoms reported were respiratory symptoms (five cases), asymptomatic (four cases), new onset seizures (two cases), fever (two cases) and pain (one case).

Age group

Twelve studies reported symptoms/signs according to age; nine studies reported symptoms in >10 patients aged <5 years[28 35 40 43 53 70 72 78 81]; two studies reported symptoms in >10 patients aged 5–10 years[53 70]; one study reported symptoms in >10 patients aged >11 years.[39]

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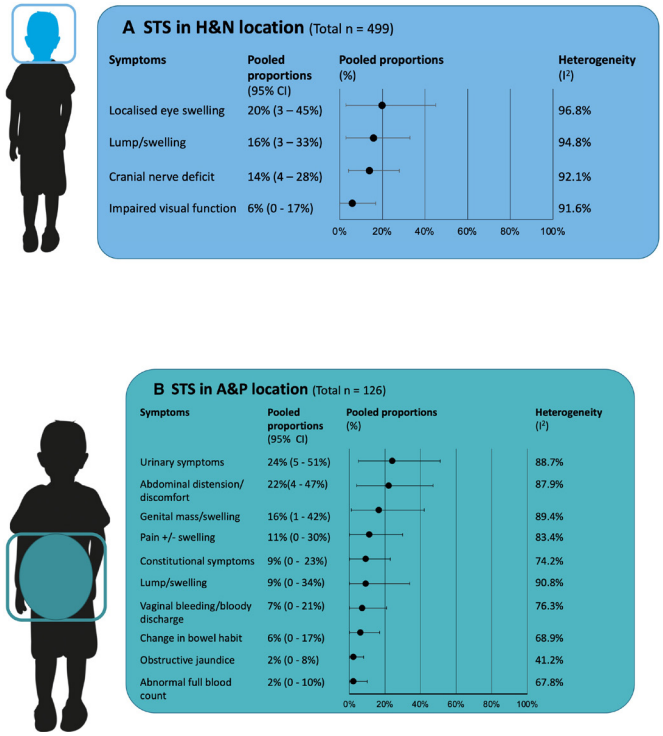

Figure 3 Pooled proportions for the most common pre-diagnostic symptoms/signs reported for soft tissue sarcomas (STS) in head and neck STS (A) and abdomen and/or pelvis STS (B).

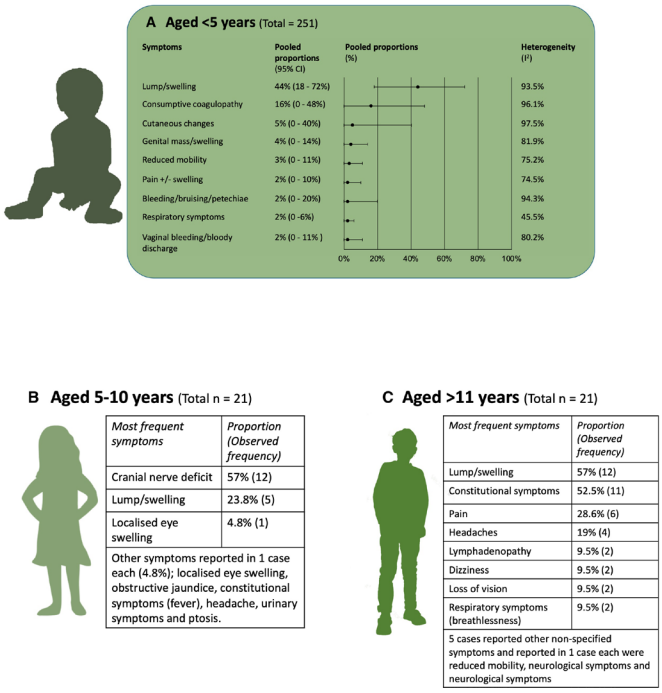

Figure 4 Pre-diagnostic symptoms/signs reported for soft tissue sarcoma (STS) by age group. Pooled proportions for ages <5 years (A), and proportions based on observed frequencies for ages 5–10 years (B) and ages >11 years (C), where meta-analysis was not conducted due to the limited number of eligible papers. *Only two papers reported symptoms in ages 5–10 years and one paper in ages >11 years, therefore no meta-analysis was carried out in either category.

Ages <5 years

Among the nine studies (n=251) with patients aged <5 years, the most common symptoms/signs were lump/swelling (44%), consumptive coagulopathy (16%), cutaneous change (5%), genital mass/swelling (4%), reduced mobility (3%), pain (2%), bleeding/bruising/petechiae (2%), respiratory symptoms (2%) and vaginal bleeding or bloody discharge (2%) (figure 4A). Bleeding/bruising/petechiae, consumptive coagulopathy and cutaneous changes were more frequent in cases aged <1 year (60/60, 107/109 and 92/95 cases, respectively).

Ages 5–10 years

Only two studies (n=21) reported >10 patients aged 5–10 years. Due to the limited sample in this age group subanalysis was not conducted rather the symptoms are outlined descriptively, (figure 4B).

Ages >11 years

One study outlined self-reported symptoms for >10 patients aged >11 years (n=21). This was an analysis of the multi-centre BRIGHTLIGHT cohort study, including ages 12–24 years, for the purpose of this review, only symptoms specific to cases aged <18 years are included (figure 4C).[37]

Exclusion of patients with Kaposi's sarcoma

Kaposi's sarcoma (KS) is rare outside of high HIV-prevalent countries. The studies reporting patients with KS were excluded to explore the robustness of the results and explore their widespread applicability, irrespective of varying KS prevalence.[32 39 49] Exclusion of patients with KS from the cohort resulted in the pooled proportions (and 95% CIs) for abnormal full blood count reducing from 2% (95% CI 0 to 6%) to 1% (95% CI 0 to 3%) and cutaneous changes from 4% (95% CI 0 to 9%) to 2% (95% CI 0 to 6%). Exclusion of KS from the other subanalysis did not change results.

DISCUSSION

This review reports the largest cohort of children with STS in all anatomical locations and ages at diagnosis. The overall results reflect previous literature that a non-specific lump/swelling and/or pain is the most commonly cited presentation of childhood STS.[9–11] However, we noted that symptoms/signs differed according to tumour location and age. Restricting our understanding of how STS presents to a non-specific lump/swelling is not sufficient to effectively achieve earlier recognition. Given that STS has the second longest TTD, our results suggest the need to tailor early diagnosis campaigns to account for age-specific and location-specific symptomatology.

Tumour locations

Subanalysis results revealed location-specific symptoms in a large cohort of children, which may have been less frequently reported and therefore lost in significance among smaller samples, highlighting the deleterious impact on data when grouped together. For those with little experience recognising STS, an awareness of these location-specific symptoms, for example, localised eye swelling or cranial nerve deficit, will be advantageous in guiding clinical suspicion and prompting earlier referral for diagnosis.

Age at diagnosis

While the limited numbers across different age subgroups in this cohort prevented further comparisons, the most frequent symptoms appeared to vary according to age. For example, genital mass/swelling was limited to children aged <5 years, while

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lymphadenopathy and headaches were solely reported in >11 years. As shown in previous literature, tumour location varies significantly with age.[5 17] This age-related variation in tumour location is also associated with the presentation of different STS subtypes at different ages. Rhabdomyosarcomas which develop from skeletal muscle have the highest prevalence in ages <5 years; however, non-rhabdomyosarcoma STS which develop from other soft tissues are strongly associated with ages <1 year and >10 years.[5 17] Rhabdomyosarcoma tends to develop in the pelvis and genitourinary region in ages <5 years.[5] The relatively high frequency of genital mass/swelling reported <5 years in our results reflects this clearly.[5] In previous literature, STS in the head/neck and intra-abdominal region was more common in <10 years, whereas extremity and intrathoracic STS was observed more in >11 years.[17]

The variation in presentation according to age is emphasised by the association between certain symptoms, bleeding/bruising/petechiae, consumptive coagulopathy and cutaneous changes, and diagnosis <1 year. Of note, there was a strong relationship between these symptoms and a subtype of STS, kaposiform haemangioendothelioma, depicting the tendency for different subtypes at different ages and perfectly illustrating the value in exploring these age-specific clinical presentations of STS.

Similar to other childhood cancers, it is plausible that the development of STS in different age-related locations is correlated with age-determined physiological growth rate of developing soft tissues.[18 19] This variation in the physiological growth rate may also explain why certain STS subtypes and locations are more prevalent in certain age groups and underpin this age-specific variation in clinical presentation of STS.

Additionally, the disparity in how attention is drawn to symptoms and signs in children of different ages cannot be ignored. A 16 years old would be able to describe their symptoms more clearly compared with a child <5 years. It is therefore important to stratify symptoms by age when studying clinical presentations of illnesses in future studies.

Strengths and limitations

These data provide an overview of the clinical presentation in the largest cohort of children diagnosed with STS, encompassing studies from 32 countries with different income levels and clinical contexts. The comprehensive approach used and inclusive nature of the eligibility criteria instils confidence that these data extensively outline current literature in this field.

A weakness of the study lies in the high heterogeneity (I^2>90%) among the studies and broad CIs of the pooled proportions. There were significant disparities in the number of recorded symptoms, and the descriptions of these symptoms varied. Symptoms not reported were assumed to be absent in our analyses. Ideally, future studies would clearly predetermine a standardised level of reported symptoms and signs to allow full transparency.

Furthermore, symptoms/signs in the studies are determined by the timing of presentation or diagnosis and most studies included data from hospital medical records at diagnosis or immediately postdiagnosis. This data is subject to potential bias and lacks primary care data. Most symptomatic patients initially present to their GP and symptoms/signs change and progress over time, so exploring the chronology of symptom development including primary care records would be of benefit.

While the results show that some clinical presentation differs by subgroup, the small sample sizes in individual studies also contribute to the high heterogeneity. This uncertainty limits any definitive conclusions to be drawn when comparing the rank of individual symptoms. Therefore, it is essential to interpret the findings carefully, viewing them as indications of patterns to avoid overinterpretation.

Implications of findings

A contributing factor to the unequal burden of childhood cancer globally is the inequity of awareness and clinical experience among the public and clinicians who are expected to recognise STS. This contributes to longer TTD or in some cases no diagnosis at all.[80] Raising awareness of the more specified, localised symptoms identified in this research will be beneficial for accurately guiding clinical suspicion and prompting earlier recognition and referral. These findings will be crucial to informing future clinical guidelines and subsequent awareness campaigns, such as Child Cancer Smart, aiming to reduce the TTD of STS and improve outcomes for children. Given the non-specificity of symptoms, while raising awareness of the symptoms is a crucial step towards improving early diagnosis, other measures such as access to diagnostic imaging will also be important to accelerate diagnosis.

CONCLUSIONS

These findings indicate that clinical presentation with childhood STS is location and age-specific. Raising awareness of this finding has the potential to facilitate early recognition, reduce TTD, improve survival and reduce disease and treatment-related morbidity for these children and young people. The limitations of these clinically significant findings are determined by the quality of the included studies. Further research is warranted to clarify age-specific clinical presentations and the chronology of symptom development.

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Supplementary material

Table S1. Diagnoses included within International Classification of Childhood Cancer (ICCC), Recode International Classification of Diseases for Oncology (ICD-O-3)/World Health Organisation (WHO) 2008, IX. Soft tissues and other Extra-osseus Sarcomas.

IX. Soft tissues and other Extra-osseus Sarcomas	
(a) Rhabdomyosarcomas	
(b) Fibrosarcomas, peripheral nerve sheath tumours, and other fibrous neoplasms	(b.1) Fibroblastic and myofibroblastic tumours (b.2) Nerve Sheath Tumours (b.3) Other fibromatous neoplasms
(c) Kaposi sarcoma	
(d) Other specified soft tissue sarcomas	(d.1) Ewing tumour and Askin tumour of soft tissue (d.2) Peripheral neuroectodermal tumour (pPNET) of soft tissue (d.3) Extrarenal extrahepatic rhabdoid tumour (d.4) Liposarcomas (d.5) Fibrohistiocytic tumours (d.6) Leiomyosarcomas (d.7) Synovial sarcomas (d.8) Blood vessel tumours (d.9) Osseous and chondromatous neoplasms of soft tissue (d.10) Alveolar soft parts sarcoma (d.11) Miscellaneous soft tissue sarcomas
(e) Unspecified soft tissue sarcomas	

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Table S2. Quality assessment tool - combined modification of crucial methodological domains used in pre-existing quality assessment tools for observation studies Critical Appraisal Skills Programme (CASP), Joanna Briggs Institute (JBI) critical appraisal tool, and Newcastle Ottowa Scale (NOS).

Methodological domains		**Specific questions**
Recruitment period		Not applicable
Number of institutions		Not applicable
Sample selection	Study population	Was study population (inclusion/exclusion criteria) clearly specified? Were the reasons for exclusion reported and consistently applied?
	Sample strategy	Selection process – convenience sample, consecutive, etc.
Case definition	Standard definition of diagnosis	Were specified diagnostic criteria consistently applied?
	Verification of diagnosis	Did all patients receive biopsy to verify diagnosis or was it a clinical diagnosis?
Ascertainment of data	Source of data	Not applicable
	Management of missing data	Not applicable
Quality of reporting	Report type	Full text or conference abstract
	Level of symptom detail reported	Number of symptoms reported, were symptoms pre-specified? How was it decided which symptoms to report?

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Table S3. Comprehensive findings from quality evaluation

Authors	Study population	Sample strategy	Case definition and verification	Type of report	Level of symptom detail reported
Abdel Wahab et al.	All patients <20 years with DFSP requiring biopsy/surgery	All consecutive patients during specified study period	Yes	Full text article	Limited symptom (2)
An et al.	Patients <18 years treated for MPSNT	Unclear sampling strategy	Yes	Full text article	Raw data reporting presenting symptoms for individual patient symptoms
Fortunati et al.	Patients <18 years treated for Desmoid fibromatosis	Unclear sampling strategy	Not reported	Conference abstract	Limited symptoms (1)
Hu et al.	Patients <18 years with AIMT	Unclear sampling strategy	Not reported	Conference abstract	Extensive symptom list (>4)
Benesc et al.	Patients<18 years with intracranial STS	Review of international registry/database for patients during specified study period. Exclusion criteria clear.	Yes (and 17 of the cases also had central pathological review)	Full text article	Raw data including individual patient symptoms
Bots et al.	Patients <18 years with STS	All consecutive patients during specified study period	Yes	Full text article	Extensive symptoms reported (>4)
Bottcher et al.	Patients <18 years with H&N rhabdomyosarcoma	Unclear sampling strategy	Not reported	Conference abstract	Limited symptoms (2 prespecified)
Boutroux et al.	Patients <20 years with orbital rhabdomyosarcoma	Unclear sampling strategy	Yes (and all cases had central pathological review)	Full text article	Extensive symptom reported (>4)
Bravo-Ljubetic et al.	Patients <18 years with H&N rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Full text article	Symptoms (4) reported
Cai et al.	Patients <18 years with rare STS (FS, SS, ERRT, ASPS, DSRCT, UDS)	All consecutive patients during specified study period, reasons for exclusion clear	Yes	Full text article	Symptom list (4) reported
Cox et al.	Patients <18 years treated for Kaposi's Sarcoma	All consecutive patients during specified study period	Diagnosed clinically and using biopsy where possible	Full text article	Extensive symptom list >4
Croteau et al.	Patients <18 years with Kaposiform haemangioendothelioma	All consecutive patients during specified study period, reasons for exclusion clear	Clinical diagnosis based on expert team consensus (including biopsy in 62 cases)	Full text article	Extensive symptom list >4

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de Carvalho et al.	Patients <18 years with any H&N STS	All consecutive patients during specified study period, reasons for exclusion clear	Yes	Full text article and raw data	Raw data including individual patient symptoms
Dehner et al.	Patients <18 years with rhabdomyosarcoma confined to the uterine cervix	All consecutive patients during specified study period	Yes	Full text article	Descriptive report of individual patient symptoms
Demir et al.	Patients <18 years with MPNST	All consecutive patients during specified study period	Not reported	Full text article	Symptoms list (4) reported
Deyrup et al.	Patients <20 years with malignant cutaneous angiosarcoma	All consecutive patients during specified study period	Yes	Full text article	Symptoms list (4) reported
Diaconescu et al.	Patients <18 years with rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Full text article	Symptoms list (4) reported
Dombrowski et al.	Patients <20 years with head & neck rhabdomyosarcoma, excuding orbital	All consecutive patients during specified study period	Yes	Full text article	Limited symptom reported (1)
El-Mallawany et al.	HIV-infected patients <18 years with KS	All consecutive patients during specified study period	Diagnosed clinically and using biopsy where possible	Full text article	Extensive symptom list (>4) reported
El-Nadi et al.	Patients <18 years with orbital rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Full text article	Extensive symptom list (>4) reported
Fasina et al.	Patients <18 years with opthalmic rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Conference abstract	Symptom list (3) reported
Fernandez-Pineda et al.	Patients <18 years with vaginal rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Full text article & raw data	Raw data reporting individual patient symptoms
Ferrari et al.	Patients <21 years with any previously untreated soft tissue sarcoma	All consecutive patients identified on institutions database during specified study period, reasons for exclusion clear	Yes	Full text article	Limited symptoms (1) reported
Giuseppucci et al.	Patients <18 years with lung inflammatory myofibromatosis	Unclear samplig strategy	Yes	Full text article	Extensive symptom list (>4) reported
Hausler et al.	Patients <18 years with rhabdomyosarcoma of head & neck	Review of national database, cancer registry and institutions database for consecutive cases duinrg specified study period, reasons for exclusion clear	Yes	Full text article	Extensive symptom list (>4) reported
Hemida et al.	Patients <18 years with rhabdomyosarcoma of the female genital tract	Unclear sampling strategy	Yes	Full text article	symptom list (3) reported
Hessissen et al.	Patients <15 years with rhabdomosarcoma	All consecutive patients during specified study period	Yes	Full text article	Extensive list symptoms >4 reported

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Ibikunle et al.	Patients <20 years with rhabdomyosarcoma of head&neck region	All consecutive patients identified in chart review during specified study period	Yes	Full text article	Limited symptom list (1) reported
Iqbal et al.	Patients <18 years with DFSP	All consecutive patients identified in chart review during specified study period, reasonsfor exclusion clear	Yes	Full text article & raw data	Raw data reporting individual patient symptoms
Ji et al.	Patients <18 years with vascular tumou/Kaposiform haemangioendothelioma without cutaneous manifestations	Review of central pathology database and all centrerecords, including all consecutive cases during study period, reasons for exclusion clear	Overall clinical diagnosis and biopsy for all cases	Full text article & raw data	Raw data reporting individual patient ymptoms
Kadhim et al.	Patients <21 years with any soft tissue sarcoma in the pelvis (excluding testicular, visceral pelvic, or prostate)	Review of tumour registry database and institution records, all consecutive patients identified during study period, exclusion criteria clear	Yes	Full text article	Extensive list of symptoms (>4) reported
Karamercan et al.	Patients <16 years with NRSTS	Unclear sampling strategy	Not reported	Conference abstract	limited symptoms l(1) reported
Koo et al.	Patients <18 years with any STS	Review of cancer registry database for all patients during specified study period, exclusion criteria clear	Not eported	Full text article & raw data	Combination of extensive prespecified symptoms (>4) & other symptoms reported by patient
Lim et al.	Patients <18 years with rhabdomyosarcoma of bladder/prostate	All consecutive patients identified during study period, exclusion criteria clear	Not reported	Conference abstract	Extensive symptom list (>4) reported
Livio et al.	Patients <18 years with rhabdomyosarcoma of the orbit	Unclear sampling strategy	Not reported	Conference abstract	imited symptom (1) reported
Maher et al.	Patients <18 years with any intracranial soft tissue sarcoma	All consecutive patients identified during review of hospital database during specified study period	Yes	Full text article & raw data	Raw data reported including individual patient symptoms
Mathey et al.	Patients <1 year with any soft tissue sarcoma	All consecutive patients identified during chart review during specified study period	Not reported	Conference abstract	Limited symptom (1) reported
Missaoui et al.	Patients <15 years with any soft tissue sarcoma	Review of national cancer registry and pathological database	Yes	Full text article	Extensive symptom list (>4) reported
Okumu et al.	Patients aged <15 years with any soft tissue sarcoma of orofacial region	All consecutive patients identified during chart review during specified study period	Yes	Full text article	Reporting limited to clinical sign list (3)

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Papillard-Marechal et al.	Patients <18 years referred with soft tissue mass, subsequently diagnosed as malignant	All consecutive patients referred to or sent to centre for second opinion during specified study period	Unclear	Full text article	Prespecified symptoms (3) reported
Parida et al.	Patients diagnosed with infantile fibrosarcoma	All consecutive patients identified during chart review during specified study period	Yes	Full text article	imited symptom list (1) reported
Perruccio et al.	Patients <18 years with rhbdomyosarcoma of biliary tract	Review of national cancer protocol registry, exclusion criteria clear	Yes and all cases had a central pathological review	Full text article	Raw data reported including individual patient symptoms
Pinheiro et al.	Patients <18 years with any soft tissue sarcoma	Unclear sampling strategy	Not reported	Conference abstract	Limited symptoms (1) reported
Posso-De Los Rios et al.	Patients <18 years with DFSP	All consecutive patients identified during chart review during specified study period	Yes	Full text article	Symptom list (3) reported
Reilly et al.	Patients <18 years with rhabdomyosarcoma of H&N region	Review of general oncology database and hospital database for all consecutive patients during specified study period.	Not reported	Full text article	Limited symptoms (1) reported
Rifi et al.	Patients <18 years with rhabdomyosarcoma	Unclear sampling strategy	Not reported	Conference abstract	Limited symptoms (1) reported
Ronghe et al.	Patients <18 years with rhabdomyosarcoma	All consecutive patients identified during review of institutions database during specified study period	Not reported	Conference abstract & poster	Extensive symptom (>4) list reported
Sachedina et al.	Female paediatric patients <18 years with urogenital rhabodmyosarcoma	All consecutive patients identified during review of institutions pathology database during specified study period	Yes	Full text article	Reported individual patient symptoms
Shi et al.	Patients <18 years with abdominal rhabdoyosarcoma not of organ origin	All consectuvie patietns during specififed study period, exclusin criteria clear	Overall clinical diagnosis and biopsy for all cases	Full text article	Extensive symptom list (>4) reported
Siwillis et al.	Patients <18 years with any soft tissue sarcoma	All consecutive patients during specified study period	Yes	Full text article	symptom list (2) reported
Stefan et al.	Patients <14 years diagnosed with KS and HIV-infection	Review of national database for all consecutive patients diagnosed and treated for KS	All cases confirmed with biopsy except 1	Full text article	Extensive symptoms list (>4) reported

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Tsai et al.	Patients <18 years with DFSP	All consecutive patients during specified study period	Yes	Full text article	limited symptom (2) list reported
Varan et al.	Patients with NF1 <18 years with any soft tissue sarcoma	All consecutive NF1 patients during specified study period	Yes	Full text article & Raw data	Raw data reported including individual patient symptoms
Wang et al.	Patients <18 years with alveolar soft part sarcoma	All consecutive patients during specified study period	Yes	Full text article & Raw data	Raw data reported including individual patient symptoms
Zhang et al.	Patients <18 years with rhabdomyosarcoma of H&N region	All consecutive patients during specified study period	Yes	Full text article	Symptom list (4) reported
Zhao et al.	Patients <18 years with rhabdomyosarcoma	All consecutive patients during specified study period	Yes	Full text article & raw data	Raw data reported including individual patient symptoms
Zorzi et al.	Patients <18 years with rhabdomyosarcoma in H&N region	All consecutive patients during specified study period	Yes	Full text article	Limited symptom (1) reported
Hu et al.	Patients <18 years with kaposiform haemangioendothelioma	All consecutive patients during specified study period, those with incomplete data/investigations were excluded	Yes	Full text article	Extensive symptom (>4) list reported
Valdivielso-Ramos et al.	Patients <18 years with DFSP	All consecutive patients during specified study period were included	Yes	Full text article & raw data	Raw data reported including individual patient symptoms