Epidemiology, incidence, and survival of synovial sarcoma of children: a SEER database analysis

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Background: Roughly 5% to 10% of soft tissue sarcomas fall under the category of synovial sarcomas (SSs), a rare and malignant tumor originating from soft tissues with unclear differentiation, primarily affecting teenagers and young adults. The goal of this study was to assess the latest survival rates for SS of children and the risk factors affecting survival using the Surveillance, Epidemiology and End Results (SEER) database.

Methods: Age, sex, race, SEER stage, surgery, radiation, chemotherapy, laterality, site of SS, and survival time were collected in the SEER database for survival and prognostic factor analysis. The overall survival curves and cancer special survival were obtained by Kaplan-Meier according to different factors. A multivariate Cox regression model and a predictive nomogram have also been constructed.

Results: A total of 130 patients were enrolled in the study. In the overall survival analysis, age (P=0.01), male (P=0.04), no surgery (P<0.01), chemotherapy (P<0.01), primary tumor site in soft tissue (P=0.02), and in distant of SEER stage (P<0.01) were associated with a worse prognosis in children with SS. Multivariate analysis showed that chemotherapy and in distant of SEER stage were independent indicators of unfavorable prognosis. A similar result was released in the specialized cancer survival analysis. A nomogram was used to predict the prognosis of SS in children and a calibration curve was used to validate the nomogram prediction against the actual observed survival outcomes.

Conclusions: In summary, chemotherapy, and worse SEER stage were associated with poorer overall and cancer special survivals. Nomogram was able to predict the probability of 1-, 5- and 10-year overall survivals and showed good consistency with the actual observed outcomes.

Keywords: Synovial sarcoma (SS); Surveillance, Epidemiology and End Results (SEER); survival; children

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Introduction

Soft tissue sarcomas are a class of diverse mesenchymal tumors that differ in their clinical behavior and responsiveness to therapy (1-3). About 5% to 10% of soft tissue sarcomas are synovial sarcomas (SSs), a very uncommon malignancy that represents a soft tissue sarcoma of unclear differentiation and usually affects teenagers and young adults (4). A chromosomal aberration called T (x;18) (P11.2;q11.2), which results in the development of SS18-SSX Fusion oncogenes, is a largely accepted etiological etiology for SS. Since it is present in more than 90% of SS cases, this chromosomal abnormality is thought to be the root cause of SS (5). Since SS is frequently seen in the lower extremities, particularly in the thigh region, it is possible to perform a complete resection (6). The prognosis is influenced by the tumor's depth, size, and location (7). However, prior studies of SS have documented a variety of patient outcomes, with the 5-year overall survival ranging from 44% to 76%. SS is typically thought to be a high-grade tumor with a dismal prognosis (8,9).

Children and teenagers have the highest incidence of SS, as was already mentioned. However, due to the low morbidity, it is difficult to determine how many pathogenic variables, particularly for young people, affect SS survival. Around 34.6% of Americans are represented in the Surveillance, Epidemiology, and End Results (SEER) database, which compiles data on cancer incidence from 18 national cancer registries (10). The SEER database started collecting data in 1973 and has since collected information on patient demographics, main anatomic tumor site,

tumor morphology and stage at diagnosis, treatment, and vital status follow-up (11). The SEER database is useful for examining tumors, especially rare tumors as SS, with sufficient statistical power and population level due to its extensive multi-institutional data collection (12). Data examining the variations in demographic propensities and prognosis of SS in children and adolescents through the national database are currently scarce. Our goal was to examine epidemiologic and prognostic data of children and adolescents with SS in order to better understand and treat this condition in this population. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-59/rc).

Methods

Clinical data and selection criteria

We selected a database in the program named "SEER research plus data, Nov. 2020 Sub (2000–2018)" that comprised information on SS patients' course of treatment, including chemotherapy and radiation therapy. Based on the following inclusion criteria, we ultimately chose 130 cases from the SEER database: (I) patients with SS who have been diagnosed using the third version: International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (13); (II) between 2000 and 2018, diagnoses were made for all cases; (III) the sole primary malignant tumor discovered to date; (IV) histological codes: 9040/3; (V) clinical information in its entirety, including age, gender, ethnicity, SEER stage, cancer-directed surgery, radiation, chemotherapy, and primary site; (VI) complete follow-up and knowledge of survival time; (VII) less than 19 years old.

Study variables

Age at diagnosis, sex, race, SEER stage, cancer-directed surgery, radiation, chemotherapy, and primary site were the characteristics we considered in the study. The age upon diagnosis was broken down into fewer than 5, 5–9, 10–14, and 15–19 years old categories. Sex included male and female. The race classifications were White, Black, Asian, and American Indian. Localized, regional, and distant were all parts of the SEER stage. Patients received either surgical, radiation, or chemotherapy treatment. The major location was categorized as either soft tissues or others.

Highlight box

Key findings
• Chemotherapy and in distant of Surveillance, Epidemiology, and End Results (SEER) stage were associated with poorer overall survival rates in patients with synovial sarcoma (SS).

What is known and what is new?
• About 5–10% of soft tissue sarcomas are SSs, is a uncommon type of tumor.
• Factors such as male, primary tumor site in soft tissue, chemotherapy treatment, in distant of SEER stage, and the absence of surgery were associated with a poorer prognosis in children with SS.

What is the implication, and what should change now?
• For SS, surgical treatment is crucial. Chemotherapy and radiotherapy do not seem to be as recommended as traditionally thought.
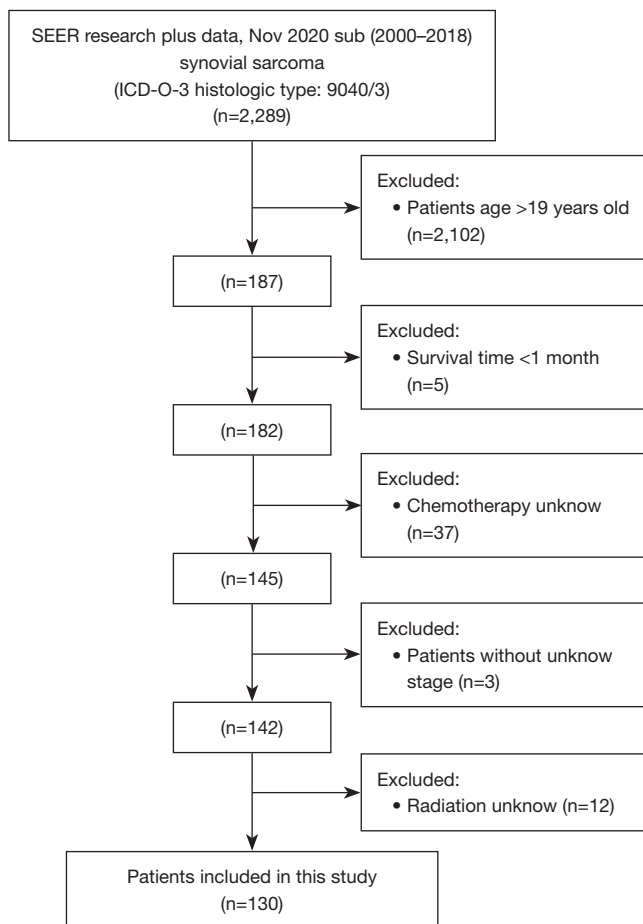

Figure 1 The flow chart for selection of study population. SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, international classification of diseases for oncology, 3rd edition.

The endpoint of interest was overall survival, which was determined as the interval between diagnosis and death from all potential causes.

Ethical statement

The study adhered strictly to the principles outlined in the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Children's Hospital of Soochow University (No. 2023021). As the anonymous patient data is from the publicly available SEER database, individual consent was not required for this research.

Statistical analysis

R version 4.0.2 (https://www.r-project.org/) and IBM

SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) were used to conduct the statistical analysis. Frequencies and percentages were used to present categorical variables. Each variable underwent Kaplan-Meier survival analysis, a log-rank test was used to assess the significance of the variations in survival curves, and Landmark analysis was applied if the survival curves crossed. To identify the characteristics that increase the likelihood of survival, multivariate Cox regression was used. Statistical significance was defined as a two-sided P value no more than 0.05. The nomogram model was created to forecast how SS might turn out. The nomogram underwent internal validation, and the model's discrimination and calibration were assessed as well. This article's assessment of discrimination was based on the concordance index (C-index). If the C-index is less than 0.5, the model has no predictive potential. A C-index of l means that the model's forecasts and the observed data agree completely. The calibration plot method, which compares the event incidence predicted by the nomogram model to the actual incidence, was used to assess the degree of calibration.

Results

Patient baseline characteristics

We gathered information on all patients with SS diagnosed between 2000 and 2018 using the SEER database. Analysis of SEER research plus data, Nov. 2020 Sub (2000–2018). There were 2,289 patients who were all given the SS diagnosis. 130 patients were subsequently included in our study after being initially screened for exclusion criteria (*Figure 1*). Among these patients, there were 69 girls and 61 boys. There were 3 children under the age of 5, 16 children aged 5 to 9, 43 children aged 10 to 14, and 68 children aged 15 to 19 years. There were 98 white people, 22 black people, and 10 people of other races (*Table 1*). There were 87 instances were localized, 29 cases were regional, and 14 cases were remote, according to the SEER stage. The majority of the patients had surgery. There were just 4 instances in which surgery was skipped. 66 patients had chemotherapy, while 80 received radiation therapy. Overall patient survival was 76.92% throughout follow-up (*Table 2*).

Prognostic factors for survival in SS

Age (P=0.01), sex (P=0.04), primary tumor site (P=0.02), SEER stage (P<0.01), chemotherapy (P<0.01), and surgery

Table 1 Baseline demographics

Characteristics	Total (n=130)
Age (years), n (%)	
0–4	3 (2.31)
5–9	16 (12.31)
10–14	43 (33.07)
15–19	68 (52.31)
Sex, n (%)	
Female	69 (53.07)
Male	61 (46.93)
Race, n (%)	
White	98 (75.38)
Black	22 (16.92)
Asian	5 (3.85)
American Indian	5 (3.85)
Laterality, n (%)	
Right	67 (51.54)
Left	63 (48.46)
Site, n (%)	
Soft tissue	125 (99.65)
Lung and bronchus	3 (0.21)
Kidney and renal pelvis	1 (0.07)
Cranial nerves	1 (0.07)
Year of diagnosis, n (%)	
2000–2004	36 (27.69)
2005–2009	45 (34.61)
2010–2014	30 (23.08)
2015–2018	19 (14.62)

Table 2 Clinical characteristics of patients

Characteristics	Total (n=130)
Historic stage, n (%)	
Localized	87 (66.92)
Regional	29 (22.31)
Distant	14 (10.77)
Chemotherapy, n (%)	
Yes	66 (50.76)
No	64 (49.24)
Radiation, n (%)	
Yes	80 (61.54)
No	50 (38.46)
Survival outcomes, n (%)	
Alive	100 (76.92)
Dead	30 (23.08)

predictors of a poor outcome (*Table 3*). We discovered similar outcomes for cancer special survival (*Table 4*). Then, we combined all the clinicopathological criteria to create a nomogram that forecasts the likelihood of overall survival for SS at 1, 5, and 10 years (*Figure 4A*). Internal testing revealed that the nomogram can predict the C-index of OS with a good degree of accuracy; it is 0.852, demonstrating strong concordance. The calibration plot revealed that the predict risk curve is extremely close to the ideal curve when comparing the predicted and actual probabilities of overall survival at 1-, 5-, and 10-year for the SS, demonstrating an excellent predictive capacity (*Figure 4B*). DCA curves showed that the nomogram could more precisely predict the 1, 5, and 10-year overall survival of SS because it included more net advantages (*Figure 4C-4E*).

Discussion

With a histologic resemblance to synovial cells, SS is a rather uncommon subtype of soft tissue sarcoma; therefore, the name (14). With a total of 2,289 patients included in this investigation, it was the largest and most recent series on SS. Additionally, 130 children and adolescents were discovered. The findings of this investigation were quite significant. Localized is ease was evident at the time of diagnosis in slightly more than half of the patients. A bad prognosis was linked to having male partners. Children
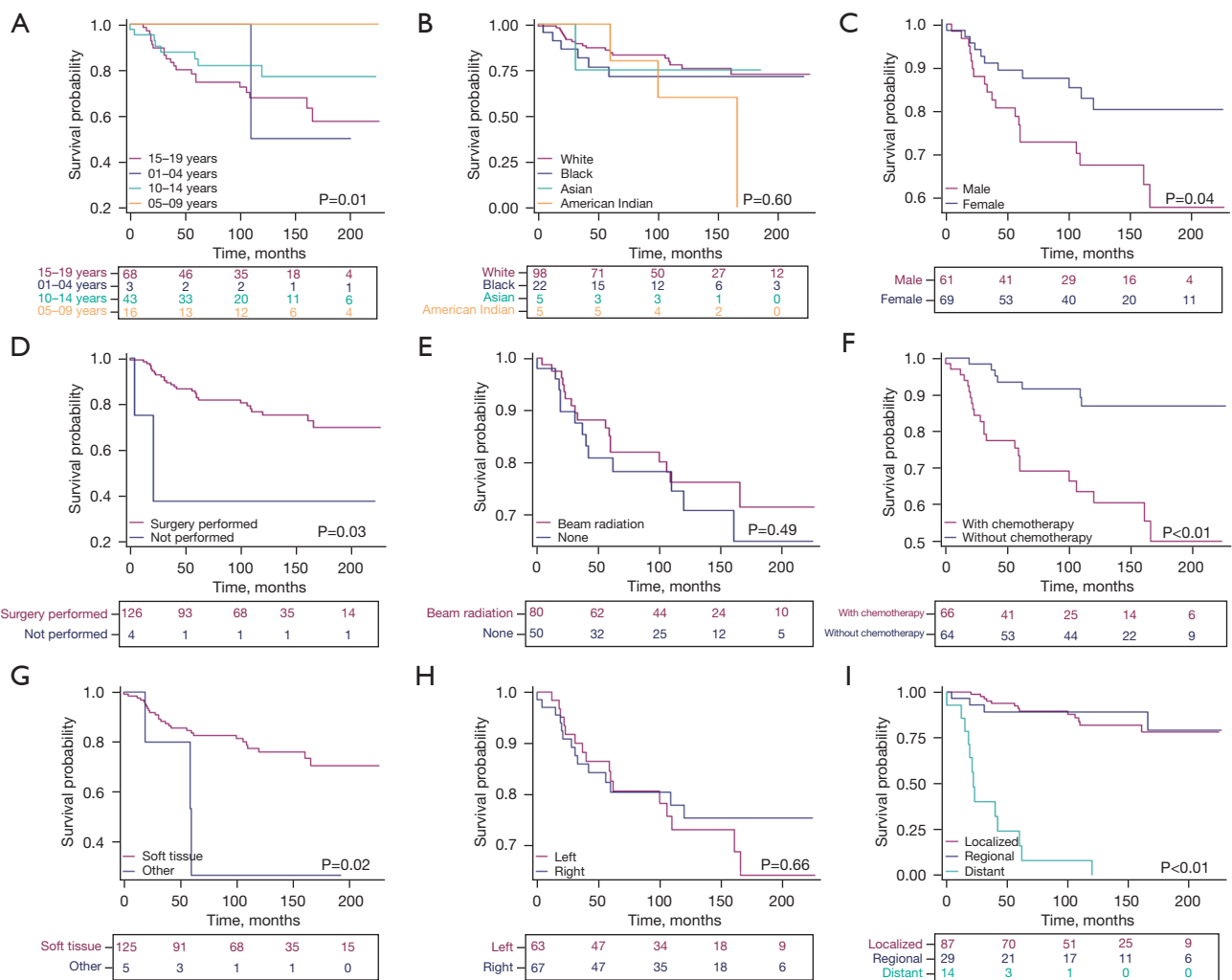
performed (P=0.03) all significantly affected overall survival, but race (P=0.60), radiation (P=0.49), and laterality (P=0.66) did not significantly affect SS survival (*Figure 2*).When the Kaplan-Meier survival analysis for cancer special survival was used, similar findings were obtained (*Figure 3*).The univariate analysis of overall survival revealed that the following factors were associated with a poor prognosis: female, chemotherapy, primary SS not affecting soft tissues, and remote from SEER stage. No treatment and being far from SEER stage were shown by the multivariate analysis to be independent

Figure 2 Overall survival Kaplan-Meier curves for SS patients. (A) Age; (B) race; (C) sex; (D) surgery; (E) radiation; (F) chemotherapy; (G) site; (H) laterality; (I) SEER stage. The meaning of the box below x-axis is number at risk. SS, synovial sarcoma; SEER, Surveillance, Epidemiology and End Results.

under the age of five were discovered to have a less favorable prognosis when age groupings were investigated. Additionally, it was shown that initial soft tissue tumors had a better prognosis. It is perplexing, nevertheless, that children who receive chemotherapy or surgery have a worse prognosis.

According to the study, 66.92% of children and adolescents who were hospitalized had localized tumors. In other words, a significant proportion of patients—up to 33.08%—were metastatic at the time of diagnosis. Additionally, it was established that metastatic spread was linked to a poor prognosis. The regional or remote spread of SS is known to be connected to poor prognosis, similar

to many soft tissue sarcomas (9). Male sex has been linked to a worse prognosis in SS, according to earlier reports (15). The present analysis corroborated the previous findings. One of the most significant prognostic factors in SS is age, as is well recognized. According to the data, patients under the age of 19 had the greatest prognosis, while those over 70 had significant fatality rates (16). When Sultan *et al.* studied SS in children and adults, they found that the prognosis for SS in adults was poorer (9). We only looked at the prognosis of SS patients aged 1 to 19 in this study, and the patients were separated into four groups. The lowest overall survival rate was observed to be among children under 5 years old. It is worth noting that the small sample
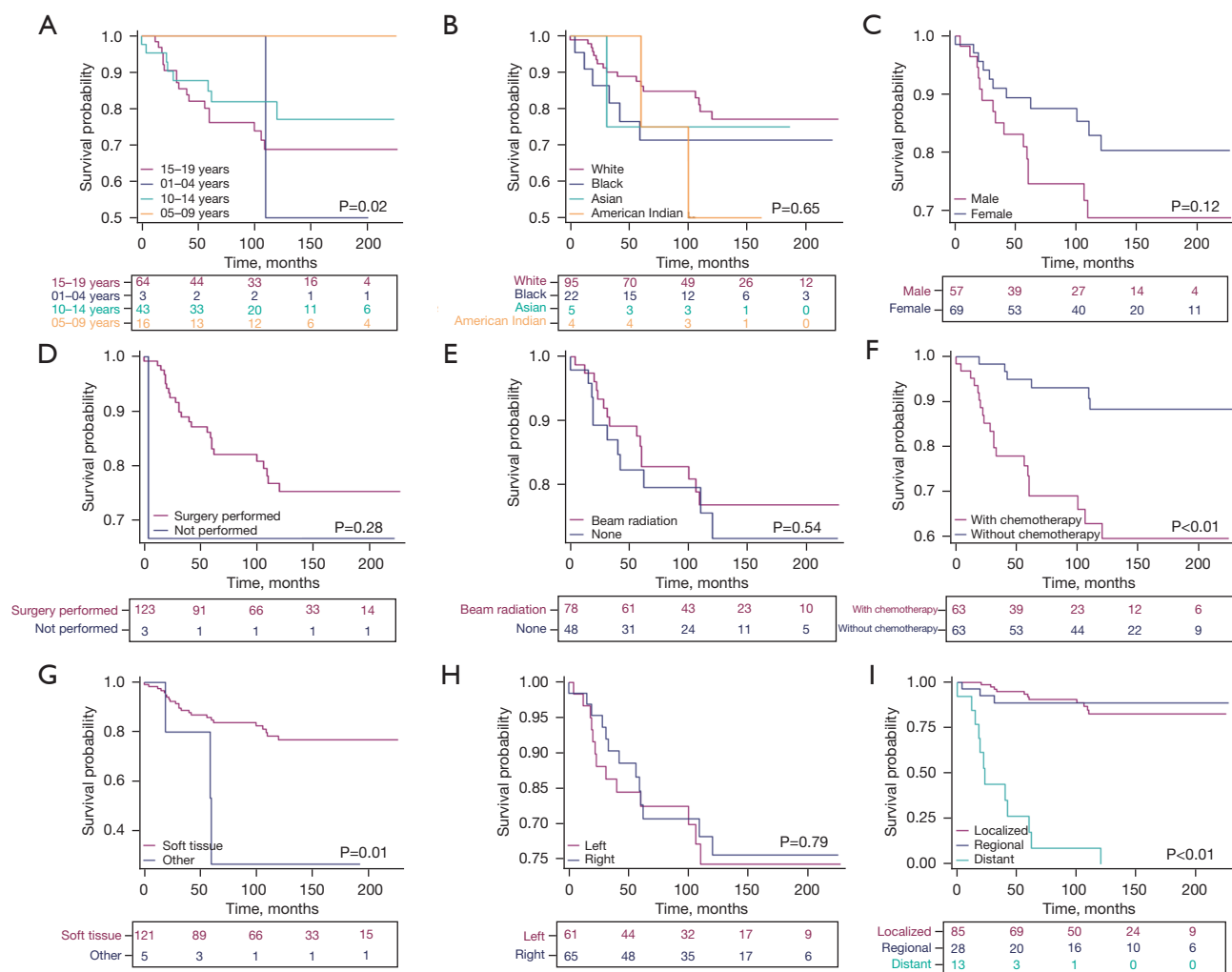
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Zhu et al. Prognostic factors for SS of children

Figure 3 Cancer special survival Kaplan-Meier curves for SS patients. (A) Age; (B) race; (C) sex; (D) surgery; (E) radiation; (F) chemotherapy; (G) site; (H) laterality; (I) SEER stage. The meaning of the box below x-axis is number at risk. SS, synovial sarcoma; SEER, Surveillance, Epidemiology and End Results.

size (n=3) for patients under the age of five may affect the accuracy and generalizability of our prognosis judgment for this group. To more accurately assess the prognosis of this age group, we believe it is necessary to expand the sample size in future studies in order to draw more reliable and statistically significant conclusions.

SS is often placed in the extremities but can also be seen in different body parts. The second most frequent location is reported as head and neck area (17). However, we found that, among SS in children, the lungs are the second most common primary site. It is similar as some other literature (14). It is known that SS located in other regions are associated with a worse prognosis than SS located in

extremities (9). In the current study, compared with soft tissue, other location tumors were found to have a worse prognosis.

According to reports, wide border resection, radiation, and adjuvant chemotherapy are the standard treatments for SS (18-20). In adults, there are limited data, there is debate about its effectiveness, and it is typically classified as low chemo-sensitive (21,22). Chemotherapy is well-defined and is known to have a high response rate in pediatric patients (23). However, we discovered that the prognosis for SS children who took chemotherapy was poorer. Similar to this, Al-Hussaini *et al.* discovered that individuals with localized SS who received chemotherapy

Table 3 Univariate and multivariate Cox analysis for overall survival for patients with synovial sarcoma (n=130)

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (years)	130				
15–19	68	Reference		Reference	
1–4	3	0.979 (0.131–7.289)	0.98	3.168 (0.366–27.425)	0.29
5–9	16	0.000 (0.000–Inf)	0.99	0.000 (0.000–Inf)	0.99
10–14	43	0.602 (0.267–1.360)	0.22	0.554 (0.224–1.369)	0.20
Sex	130				
Male	61	Reference		Reference	
Female	69	0.468 (0.223–0.985)	0.04	0.539 (0.237–1.226)	0.14
Race	130				
White	98	Reference			
Black	22	1.361 (0.546–3.391)	0.50		
Asian	5	1.087 (0.146–8.105)	0.93		
American Indian	5	2.389 (0.709–8.049)	0.16		
Surgery	130				
Surgery performed	126	Reference			
Not performed	4	4.168 (0.982–17.682)	0.05		
Radiation	130				
Beam radiation	80	Reference			
None	50	1.290 (0.626–2.656)	0.49		
Chemotherapy	130				
Yes	66	Reference		Reference	
No	64	0.231 (0.099–0.539)	<0.01	0.280 (0.108–0.725)	<0.01
Stage	130				
Localized	87	Reference		Reference	
Regional	29	0.899 (0.292–2.764)	0.85	0.904 (0.279–2.927)	0.86
Distant	14	17.698 (7.819–40.057)	<0.01	14.775 (6.070–35.961)	<0.01
Site	130				
Soft tissue	125	Reference		Reference	
Other	5	3.558 (1.074–11.790)	0.03	1.845 (0.509–6.685)	0.35
Laterality	130				
Left	63	Reference			
Right	67	0.855 (0.417–1.754)	0.67		

CI, confidence interval; Inf, infinity.

Table 4 Univariate and multivariate Cox analysis for cancer-specific survival for children with synovial sarcoma (n=126)

| Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (years)	126				
15–19	64	Reference			
1–4	3	2.032 (0.266–15.522)	0.49		
5–9	16	0.450 (0.104–1.960)	0.28		
10–14	43	0.977 (0.443–2.154)	0.95		
Sex	126				
Male	57	Reference			
Female	69	0.636 (0.306–1.323)	0.22		
Race	126				
White	95	Reference			
Black	22	1.144 (0.431–3.036)	0.78		
Asian or Pacific Islander	5	1.856 (0.433–7.945)	0.40		
American Indian/Alaska Native	4	0.955 (0.128–7.115)	0.96		
Surgery	126				
Surgery performed	123	Reference			
Not performed	3	1.746 (0.237–12.857)	0.58		
Radiation	126				
Beam radiation	78	Reference			
None	48	0.657 (0.299–1.443)	0.29		
Chemotherapy	126				
Yes	63	Reference		Reference	
No	63	0.457 (0.212–0.985)	0.04	0.639 (0.286–1.424)	0.27
Stage	126				
Localized	85	Reference		Reference	
Regional	28	0.918 (0.298–2.824)	0.88	0.970 (0.314–2.999)	0.95
Distant	13	16.627 (7.240–38.187)	<0.01	16.327 (6.979–38.193)	<0.01
Site	126				
Soft tissue	121	Reference		Reference	
Other	5	3.674 (1.106–12.207)	0.03	3.441 (0.958–12.356)	0.05
Laterality	126				
Left	60	Reference			
Right	66	0.773 (0.372–1.609)	0.49		

CI, confidence interval.
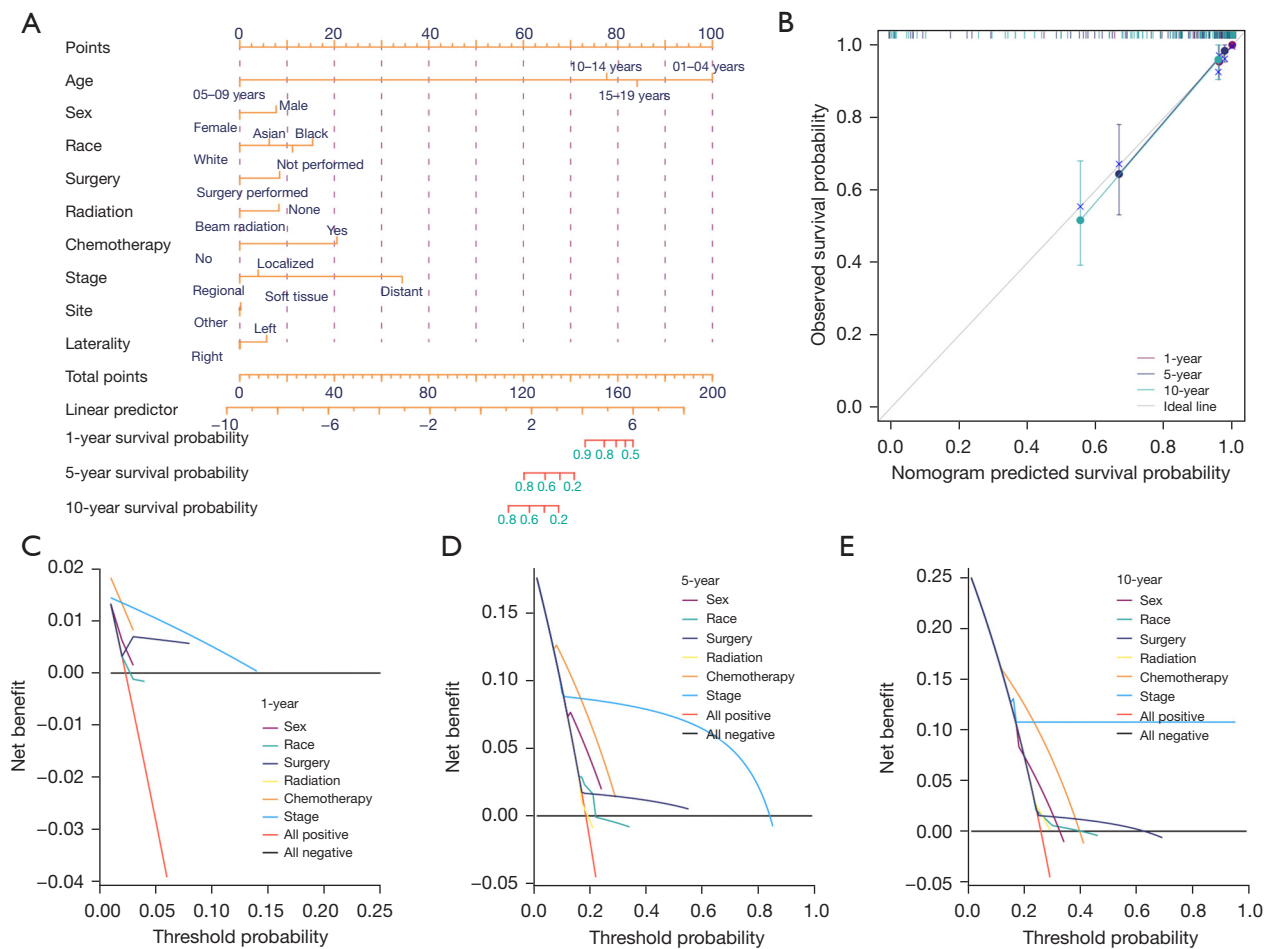
Figure 4 Construction of prognostic nomogram and validation. (A) Nomogram for 1-, 5-, and 10-year survival rates of children with SS; (B) calibration plot of a nomogram for 1-, 5- and 10-year survival rate of children with SS; (C) decision curve of the nomogram predicting ability for 1-year survival of children with SS; (D) decision curve of the nomogram predicting ability for 5-year survival of children with SS; (E) decision curve of the nomogram predicting ability for 10-year survival of children with SS. SS, synovial sarcoma.

experienced an even higher rate of relapse than those who did not (22). Additionally, research document the negative effects of sequential chemotherapy and radiotherapy (24). Chemotherapy recipients in the current study had considerably shorter survival times than non-users. This can be explained by the selection bias in chemotherapy, which is the tendency for patients receiving chemotherapy to also have concurrent metastases and a poor prognosis. Additionally, it was discovered that chemotherapy status was also an independent risk factor for survival when independent influencing factors on survival rates were explored by multivariate cox regression analysis.

It is crucial to note that this study has significant limitations. In the first place, this study was a retrospective

analysis, and even though it covered a long time period, it is challenging to glean significant information from them. Due to incomplete data, some patients could not be included in the statistical analysis because this study was based on a database. Some demographic information and information on diseases were left out. The specifics of the preoperative and postoperative therapy were not documented. Additionally, the small sample size is one of the limitations. Lastly, the SEER database does not include information on chemotherapy regimens, which may limit our in-depth understanding and accurate assessment of the differences.

Despite these drawbacks, this study still had a lot of useful information, especially when compared to studies

that only looked at outcomes from a single location because it used data from numerous facilities with a lot of patients. Additionally, it has given information about radiotherapy and chemotherapy. It is doubtful that there will be randomized controlled studies based on histology given the incidence rates of children with SS; hence the knowledge gained from studies like the current one is crucial to inform treatment choices and direct future research.

Conclusions

At the time of diagnosis, just over half of children with SS have localized disease. We come to the conclusion that a bad prognosis is connected with the male gender, being under 5 years old at the time of diagnosis, non-soft tissue localization, chemotherapy, and a worse SEER stage.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-59/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-59/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-59/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study adhered strictly to the principles outlined in the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Children's Hospital of Soochow University (No. 2023021). As the anonymous patient data is from the publicly available SEER database, individual consent was not required for this research.

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