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ORIGINAL ARTICLE

Prevalence and prognostic impact of comorbidity in soft tissue sarcoma: A population-based cohort study

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ABSTRACT

Background. Comorbidity is an important prognostic factor for survival in other cancers, but the importance in soft tissue sarcoma has not yet been clarified. The aims of this study were to examine the prevalence of comorbidity in soft tissue sarcoma patients, and estimate the impact of comorbidity on overall and disease-specific mortality.

Material and methods. Overall, 1210 adult patients with soft tissue sarcoma in the extremities or trunk wall were identified through the Aarhus Sarcoma Registry, a validated population-based database. Information on comorbidity was obtained through the National Patient Registry, and a Charlson's Comorbidity score was calculated for each patient. The prevalence of comorbidity was assessed overall, as well as according to age and year of diagnosis. Overall and disease-specific mortality rates according to level of comorbidity were computed. The prognostic value of comorbidity was estimated using crude and adjusted Cox proportional hazard models.

Results. The overall prevalence of comorbidity was 25%. The prevalence increased with increasing age, and patients with comorbidity had a larger proportion of adverse prognostic factors when compared to patients without comorbidity. The five-year disease-specific mortality was 26% (95% CI 24–29) for patients without comorbidity, compared to 33% (95% CI 24–42), 41% (95% CI 32–50), and 44% (95% CI 33–55) for patients with mild, moderate, and severe comorbidity, respectively. After adjusting for age, sex, stage, tumor size, depth, grade, surgical margin, radiotherapy, and chemotherapy, comorbidity was independently associated with an increased overall and disease-specific mortality.

Conclusion. Patients with comorbidity had significantly increased overall and disease-specific mortality compared to patients without comorbidity, even when adjusting for important prognostic factors including age.

The incidence of soft tissue sarcoma increases with age [1]. A demographic shift in the age distribution of the general population is expected in the future, resulting in more elderly patients, who more often suffer from other chronic diseases, i.e. comorbidity, which may influence the treatment strategy, and thus survival [2]. Comorbidity has proven to be an important prognostic factor for survival in other cancer types, even when adjusting for other significant factors such as age, disease stage, and treatment [3–6].

To our knowledge only two studies have investigated the impact of comorbidity on survival in soft tissue sarcoma [7,8]. These studies, including adult, high-grade, non-metastatic, primary and adult extremity or trunk soft tissue sarcoma, respectively, reported no predictive value of comorbidity when comparing patients with and without comorbidity [7,8]. However, the prevalence and prognostic impact of comorbidity has not yet been investigated in a larger population-based series of soft tissue sarcoma. The Aarhus Sarcoma Registry (ASR), a validated

population-based sarcoma registry, provides a unique possibility to examine the impact of comorbidity in a large series of soft tissue sarcoma, while adjusting for other known prognostic factors [1].

The aims of this study were to assess and describe the prevalence of comorbidity in soft tissue sarcoma patients as well as to investigate the impact of comorbidity on overall and disease-specific mortality.

Material and methods

The Danish population is approximately 5.5 million [9]. The healthcare system provides tax-supported, free of charge health care for all residents. Since 1968, all citizens in Denmark have been assigned a unique, 10-digit civil personal registration number (CPR number), allowing for linkage on an individual level throughout all Danish registries [10].

Data sources

All sarcoma patients treated at the Aarhus Sarcoma Centre between 1979 and 2008 are registered in a clinical database, the ASR [1]. The diagnostic program and treatment follow national guidelines, and decisions are made by a multidisciplinary sarcoma team [11,12]. Sarcomas were classified into three grades using the grading system described by Jensen et al. [13]. The primary treatment was surgery aiming for a wide excision, according to the principles of Enneking, followed by radiotherapy for deep-seated intermediate and high-grade sarcomas [14]. The ASR is population-based for western Denmark and includes CPR number, date of diagnosis, as well as detailed validated data on tumor characteristics, treatment, follow-up, and death. Data regarding death includes date of death, cause of death (sarcoma or non-sarcoma), and disease status at time of death (disease-free, localized disease, or metastatic disease).

The National Patient Registry (NPR) contains information on all patients admitted to Danish hospitals since 1977, including outpatient visits since 1995 [15–17]. The registry covers more than 99% of Danish hospital admissions in the period [17]. Data registered in the NPR includes CPR number, date of admission and discharge, as well as discharge diagnoses according to the eighth (before 1994) and 10th version of the International Classification of Disease (ICD-8 and ICD-10). The discharge diagnoses include both main and secondary diagnoses from admissions as well as emergency and outpatient visits.

The Danish Civil Registration system was established in 1968 and contains current and historical information on all persons living in Denmark.

Registered data includes CPR number, date of birth, residence, vital status (dead/alive), and date of death. The vital status is registered continuously and is updated on a daily basis [10].

The Danish Cause of Death Registry was initiated in 1875 as a result of the mandatory, by law, completion of death certificates for any death occurring in Denmark. The registry is based on the medical information from the death certificates and contains data on the immediate and underlying cause of death according to the ICD-8 and ICD-10 [18].

Patients

Between 1979 and 2008, 1753 consecutive patients were treated for soft tissue sarcoma at the Sarcoma Centre of Aarhus University Hospital, Denmark. Due to different biological behaviors, we excluded patients younger than 15 years, tumors not located in the extremities or trunk wall, and specific subtypes including gastrointestinal stromal tumors (GIST), kaposi sarcoma, atypical fibroxanthoma, and subcutaneous low-grade liposarcoma, i.e. atypical lipomatous tumor. The study population comprised 1210 adult patients with a soft tissue sarcoma in the extremity or trunk wall.

Comorbidity

The level of comorbidity at the time of sarcoma diagnosis was assessed using the Charlson's Comorbidity Index [19]. The Charlson's Comorbidity Index was originally developed in 1984 to predict one-year mortality in a cohort of 559 medical patients, and was later validated for 10-year mortality in 685 breast cancer patients. The index includes 19 medical conditions, which are weighted from 1 to 6 points according to their risk of mortality. These points are added to form a final score corresponding to the level of comorbidity [19]. The Charlson's Comorbidity Index has been adapted and validated for ICD-based hospital discharge data in various cancer types [20]. The ICD-codes included in the index are shown in Supplementary Table I, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.888494>.

Data from the ASR and NPR were linked through the CPR number, and for each of the 1210 soft tissue sarcoma patients identified in the ASR, all discharge diagnoses registered in the NPR, between 1 January 1977 and the date of the sarcoma diagnosis, were extracted. Based on these discharge diagnoses, a Charlson's Comorbidity Index score for each patient was computed. To eliminate non-specific symptoms or hospital admissions related to the sarcoma, all discharge diagnoses within 30 days, and all cancer diagnoses

within 90 days prior to the sarcoma diagnosis were excluded. The level of comorbidity was categorized into four groups; no (score 0), mild (score 1), moderate (score 2), and severe (score ≥ 3) comorbidity.

Mortality

Mortality was assessed as overall and disease-specific mortality. Data on death of the study population was obtained through the Danish Civil Registration system [10]. Patients were followed from the date of sarcoma diagnosis until death, emigration, or end of the study period (15 April 2013), whichever came first. Data on the cause of death was obtained primarily from the ASR and secondarily from the Danish Cause of Death Registry. Disease-specific mortality was defined as death from sarcoma or death with metastatic sarcoma, corresponding to ICD-8; 170, 171, 192.49-99 and ICD-10; C40-C41, C47, C49 in the Danish Cause of Death Registry [18].

Statistical analyses

The prevalence of comorbidity was assessed as an overall proportion, as well as according to age, sex, and calendar year of diagnosis. In order to have comparable data, the analysis of prevalence according to calendar year was confined to patients diagnosed between 1982 and 2008 including comorbidity only five years prior to the sarcoma diagnosis, excluding diagnoses from outpatient visits. The impact of comorbidity on overall and disease-specific mortality was assessed as proportion with 95% confidence intervals (CI) and presented as cumulative incidence functions. The prognostic value of comorbidity on overall and disease-specific mortality was assessed crude as well as adjusted for known prognostic factors; age (years), sex, stage at diagnosis (localized or metastatic), tumor size (cm), depth (subcutaneous or subfascial), grade (low, intermediate or high), surgical margin (intralesional/marginal or wide/radical), radiotherapy (yes or no), and chemotherapy (yes or no). The prognostic factors included in the adjusted analyses were selected a priori, based on a literature review. Age and tumor size were included in the analyses as four-knotted restricted cubic splines [21]. The Cox proportional hazard model was used and results presented as hazard ratios with 95% CI. The proportional hazard assumption was tested using log-minus-log plots. Subgroup analyses were performed according to age, sex, and calendar year of diagnosis. Homogeneity within subgroups was tested using the likelihood ratio test. Death from other causes than sarcoma was considered a competing event in the analyses of disease-specific mortality. All tests were two-sided and a p -value ≤ 0.05 was

considered significant. Analyses were performed using Stata, version 11.2.

Ethics

This study was approved by the Danish Data Protection Agency (2007-58-0010) and the Danish Health and Medicines Authority (7-604-04-2/262/KWH), and was conducted in accordance with the Helsinki Declaration.

Results

Patient characteristics and prevalence of comorbidity

Overall, 1210 adult patients were diagnosed with a trunk or extremity soft tissue sarcoma in western Denmark from 1979 to 2008. The median age at diagnosis was 59 years (range 15–95) and 52% were males. At diagnosis, 88% presented with a localized primary tumor. The patient characteristics are shown in Table I. The median follow-up in patients alive at the end of follow-up was 13.1 years, ranging from 2.8 to 34.2 years.

Comorbidity was present in 299 patients, corresponding to a prevalence of 25%. Of these, 106 (35%) patients had mild comorbidity, while 107 (36%) and 86 (29%) patients had moderate and severe comorbidity, respectively. The differences in patient characteristics, according to the Charlson's Comorbidity Index score, are shown in Table I. Generally, the presence of comorbidity was significantly associated with increased age, a larger proportion of metastatic disease at presentation, diagnosis in 1999–2008, grade 3 tumors, intralesional/marginal excision, as well as lack of treatment with radio- and chemotherapy. The prevalence of the medical conditions included in the Charlson's Comorbidity Index is shown in Table II. The most frequent condition, "Any tumor", was present in 9.9% of cases. The overall prevalence of comorbidity increased with increasing age, peaking at 88 years (43%), as shown in Figure 1A. The prevalence of mild comorbidity was highest at age 79 (13%), compared to age 95 (31%) and 75 (10%) for moderate and severe comorbidity, respectively. No significant change in the overall prevalence of comorbidity over the study period was observed (Figure 1B). However, some minor changes in the composition were seen, with a decrease in moderate comorbidity and an increase in severe comorbidity, most pronounced in the first part of the study period.

Overall mortality

The one-, five-, and 10-year overall mortality was 16% (95% CI 14–19), 41% (95% CI 38–44), and 52% (95% CI 49–55), respectively. The overall mortality is

Table I. Patient characteristics by Charlson's Comorbidity score (N = 1210).

	N (%)	Charlson Comorbidity score N (%)				P
		0	1	2	3+	
Total	1210 (100)	911 (75)	106 (9)	107 (9)	86 (7)	
Age (years)						
Median (range)	59 (15–95)	54 (15–95)	70 (16–91)	70 (19–93)	72 (19–87)	<0.001
Sex						
Female	580 (48)	433 (48)	47 (44)	53 (50)	47 (55)	0.52
Male	630 (52)	478 (52)	59 (56)	54 (50)	39 (45)	
Year of diagnosis						
1979–1988	268 (22)	222 (24)	19 (18)	19 (18)	8 (9)	0.002
1989–1998	390 (32)	302 (33)	31 (29)	33 (31)	24 (28)	
1999–2008	552 (46)	387 (42)	56 (53)	55 (51)	54 (63)	
Stage at diagnosis						
Localized	1065 (88)	813 (89)	94 (89)	87 (81)	71 (83)	0.04
Metastatic	145 (12)	98 (11)	12 (11)	20 (19)	15 (17)	
Tumor size (cm)						
Median (range)*	7 (1–35)	6 (1–35)	8 (1–30)	7 (1–29)	7 (1–26)	0.81
Location						
Subcutaneous	361 (30)	268 (29)	27 (25)	33 (31)	33 (38)	0.25
Subfascial	849 (70)	643 (71)	79 (75)	74 (69)	53 (62)	
Malignancy grade						
Low	212 (18)	174 (19)	20 (19)	6 (6)	12 (14)	0.001
Intermediate	167 (14)	140 (15)	8 (8)	11 (10)	8 (9)	
High	831 (69)	597 (66)	78 (74)	90 (84)	66 (77)	
Treatment						
Surgery†	1135 (94)	854 (94)	99 (93)	99 (93)	83 (97)	0.70
Wide/radical	792 (72)	622 (75)	63 (65)	59 (62)	48 (62)	0.004
Intralesional/marginal	303 (28)	204 (25)	34 (35)	36 (38)	29 (38)	
Radiotherapy	375 (31)	298 (33)	33 (31)	29 (27)	15 (17)	0.02
Chemotherapy	110 (9)	95 (10)	5 (5)	6 (6)	4 (5)	0.05

N, number. *Tumor size 39, 28, 2, 3, and 6 missing values, respectively. †Margin: 40, 28, 2, 4, and 6 missing values, respectively.

significantly affected by the level of comorbidity, as shown in Figure 2A. The five-year overall mortality for patients without comorbidity was 35% (95% CI 32–38), compared to 52% (95% CI 43–62), 62% (95% CI 53–71), and 69% (95% CI 59–78) for patients with mild, moderate, and severe comorbidity, respectively. The crude and adjusted analyses of comorbidity by age, sex, and calendar year at diagnosis are shown in Table III. The impact of comorbidity on overall mortality was significantly different among age groups ($p = 0.0028$), while not between sex ($p = 0.64$), nor calendar year of diagnosis ($p = 0.97$). A tendency towards comorbidity (all levels) being independently prognostic for overall mortality was seen in all age groups and collapsed results were computed. Overall; mild, moderate, and severe comorbidity were independently correlated with an increased overall mortality, compared to no comorbidity (Table III).

Disease-specific mortality

The one-, five-, and 10-year disease-specific mortality was 13% (95% CI 11–15), 30% (95% CI 27–32), and 34% (95% CI 31–37), respectively. The cumulative

incidence function of disease-specific mortality by level of comorbidity is shown in Figure 2B. The five-year disease-specific mortality was 26% (95% CI 24–29) in patients without comorbidity, compared to 33% (95% CI 24–42), 41% (95% CI 32–50), and 44% (95% CI 33–55) in patients with mild, moderate, and severe comorbidity, respectively. The crude and adjusted analyses of comorbidity by age, sex, and calendar year at diagnosis are shown in Table III. The impact of comorbidity among age groups ($p = 0.14$), sex ($p = 0.30$), and calendar year of diagnosis ($p = 0.94$) was not significantly different. Overall; mild, moderate, and severe comorbidity were independent prognostics for disease-specific mortality, corresponding to a 46%, 55%, and 204% increase in mortality rate, compared to patients without comorbidity (Table III). Moderate and severe comorbidity were not associated with an additionally increased rate compared to mild comorbidity ($p = 0.79$ and $p = 0.17$, respectively).

Discussion

In this population-based study we found an overall prevalence of comorbidity of 25%. Patients with

Table II. Overall prevalence of medical conditions in the Charlson's Comorbidity Index among soft tissue sarcoma patients in the Aarhus Sarcoma Registry (N = 1210).

Condition	N	%
Myocardial Infarct	44	3.6
Congestive heart failure	22	1.8
Peripheral vascular disease	27	2.2
Cerebrovascular disease	44	3.6
Dementia	5	0.4
Chronic pulmonary disease	47	3.9
Connective tissue disease	18	1.5
Ulcer disease	37	3.1
Mild liver disease	7	0.6
Diabetes	32	2.6
Hemiplegia	1	0.1
Moderate/severe renal disease	10	0.8
Diabetes with end organ damage	7	0.6
Any tumor*	120	9.9
Leukemia	4	0.3
Lymphoma	5	0.4
Moderate/severe liver disease	0	0.0
Metastatic solid tumor	32	2.6
AIDS	0	0.0

N, number; AIDS, acquired immunodeficiency syndrome.

*Excluding tumors in soft tissue and bone (ICD-8; 170, 171, 192.49-99 and ICD-10; C40-C41, C47, C49).

comorbidity had a significantly increased overall and disease-specific mortality compared to patients without comorbidity, even when adjusting for age and other important prognostic factors. A tendency towards comorbidity being associated with an increased mortality was observed within all subgroups. The impact of comorbidity on disease-specific mortality was consistent within all subgroups; however, the impact on overall mortality differed among the age groups.

Methodological considerations

The main strength of our study lies in the structure of the Danish healthcare system, which facilitates population-based studies with large sample sizes, complete follow-up on all patients, and the possibility of linkage, on an individual level, to clinical databases and registries.

The information on comorbidity was based on an administrative registry, the NPR. Due to the prospective registration of data in the NPR, independently of the aim of our study, the potential information bias is considered low. When using administrative registries, misclassifications or coding errors occur to some extent; however, in this case the comorbidity occurred before the sarcoma diagnosis, and any misclassification is therefore expected to be unrelated to the sarcoma, i.e. non-differential. Outpatient data was only registered in NPR after 1995, which means that minor comorbidity not requiring hospital admission would be missed in the first half of the study period.

The quality of diagnostic coding in NPR for the 19 medical conditions in the Charlson's Comorbidity Index has previously been validated. Thygesen et al. [22] reported an overall positive predictive value of 98% for the 19 conditions, using ICD-10 codes in the NPR in 1998–2007. The positive predictive value varied from 82% for diabetes mellitus with end organ damage to 100% for congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and moderate/severe liver disease, hemiplegia, moderate/severe renal disease, leukemia, lymphoma, metastatic tumor solid, and AIDS.

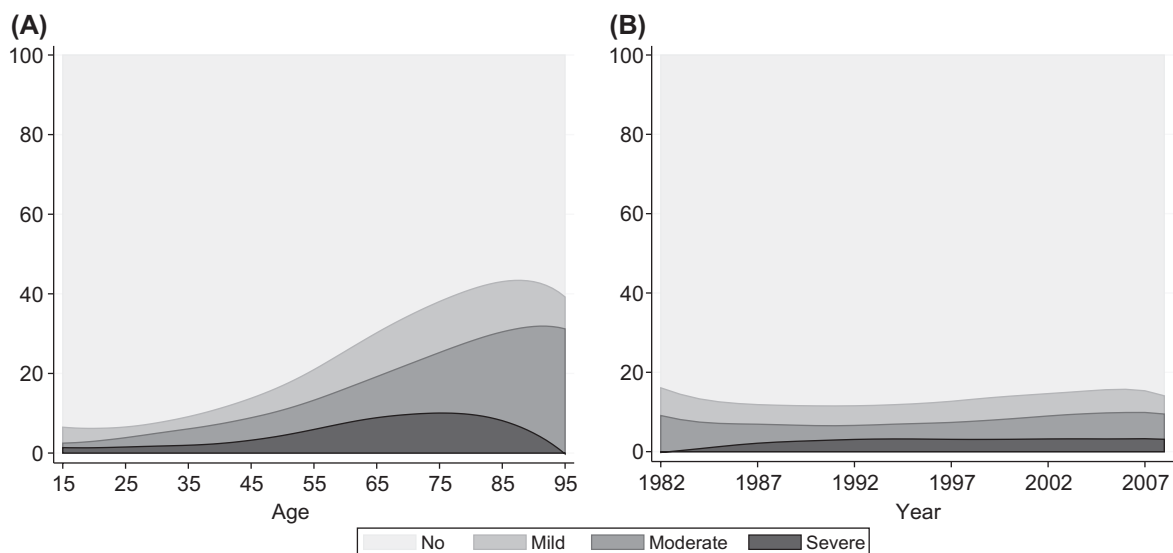


Figure 1. Prevalence of Charlson's Comorbidity score as percentage by age (A) and calendar year of diagnosis (B).

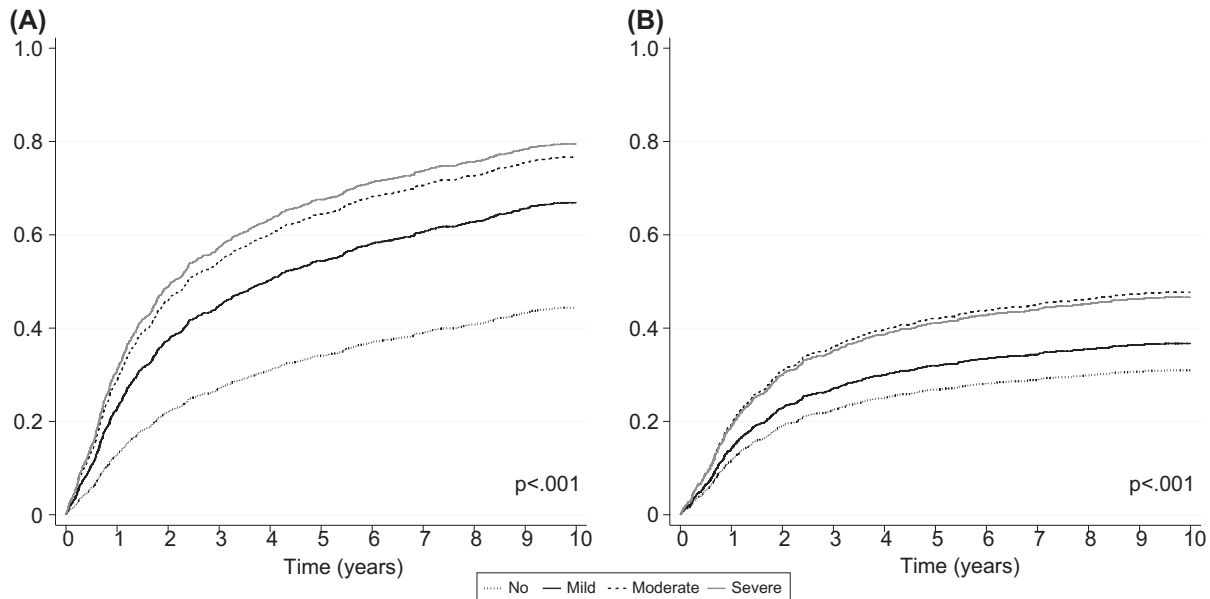


Figure 2. Cumulative incidence functions of overall (A) and disease-specific mortality (B) by Charlson's Comorbidity score.

The prevalence of some of the milder conditions, such as diabetes, might be underestimated in the NPR. The negative predictive value for ICD coding in the NPR has, to our knowledge, not been investigated; however, severe diseases with a low prevalence in a population tend to have high negative predictive value, while mild diseases with a high prevalence tend to have lower negative predictive values.

The Charlson's Comorbidity Index used to assess comorbidity is widely used, and has previously been validated [3,4,6,7,20,23]. However, the prevalence and prognosis for some of the 19 medical conditions, e.g. the condition "ulcer disease", has changed radically since the development of the index. Furthermore, some of the conditions in the Charlson's Comorbidity Index include a wide span of diagnoses with varying severity, e.g. mild and severe chronic obstructive pulmonary disease included in the condition "chronic pulmonary disease", which are weighed the same. Thus, the Charlson's Comorbidity Index might not capture the "true" mortality risk due to the individual disease, but merely the average risk of multimorbidity. Studying comorbidity as indices is often preferred in order to have sufficient statistical power; however, an update of the index in the future is relevant, especially with focus on the correlation between the level of severity and the impact on sarcoma-specific mortality. Other comorbidity indices exist, however none have proven to be superior thus far [5,24,25].

The outcome in this study was assessed as overall as well as disease-specific mortality. Overall mortality includes both deaths due to sarcoma, as well as deaths due to any other reason, whereas

disease-specific mortality only includes deaths due to sarcoma. Data on the cause of death in the Registry of Cause of Death is registered by physicians, either the deceased's general practitioner or hospital doctors, and the validity of the registered causes is thus dependent on the physicians' knowledge of preceding diseases. In patients with a preceding cancer diagnosis, the risk of stating the cancer as cause of death is increased, causing differential misclassification. Data in the ASR has been systematically validated by two experienced researchers using standardized forms [1]. Data for the cause of death was retrieved from the ASR in the majority of the cases, as the information in the ASR is suspected to be more correct than in the Registry of Cause of Death.

Prevalence

The prevalence of comorbidity was 25%. Two previous studies have investigated the prevalence of comorbidity in soft tissue sarcoma [7,26]. Nakamura et al. [7] reported an overall prevalence of 20%, while van Herk-Sukel et al. [26] reported the prevalence of medical conditions separately, e.g. 33% for cardiovascular disease, 10% for respiratory disease, and 6–7% for diabetes, anemia, and depression. A study of 27 506 newly diagnosed cancer patients, including 413 patients with musculoskeletal tumors, reported a 65% overall prevalence of comorbidity; however, this study included medical conditions not included in the Charlson's Comorbidity Index, e.g. alcohol abuse and obesity [2]. In other cancer types the prevalence of comorbidity has been reported to range from 28% to 43%, when assessed by the

Table III. Crude and adjusted analyses for the effect of comorbidity on overall and disease-specific mortality in 1210 adult soft tissue sarcoma patients by age, sex, and calendar year of diagnosis.

	N	Overall mortality			5-year (%)	Disease-specific mortality	
		5-year (%)	HR (95% CI)			Crude	Adjusted*
			Crude	Adjusted*			
Overall							
No	911	35	1	1	26	1	1
Mild	106	52	1.88 (1.48–2.41)	1.56 (1.20–2.02)	33	1.37 (0.98–1.92)	1.46 (1.01–2.10)
Moderate	107	62	2.48 (1.97–3.12)	1.55 (1.20–2.00)	41	2.06 (1.53–2.78)	1.55 (1.10–2.19)
Severe	86	69	2.70 (2.10–3.46)	2.05 (1.56–2.70)	44	2.03 (1.45–2.83)	2.04 (1.39–2.99)
15–49 years							
No	386	24	1	1	22	1	1
Mild	12	33	1.71 (0.75–3.87)	1.21 (0.52–2.84)	33	2.04 (0.90–4.65)	1.43 (0.60–3.44)
Moderate	17	59	3.53 (1.99–6.26)	2.99 (1.53–5.84)	59	3.85 (2.11–7.01)	3.20 (1.57–6.54)
Severe	8	40	2.46 (1.00–6.02)	8.77 (2.57–29.87)	38	1.65 (0.52–5.19)	10.77 (2.30–50.35)
50–69 years							
No	322	33	1	1	27	1	1
Mild	41	39	1.28 (0.84–1.95)	1.86 (1.18–2.91)	29	0.91 (0.50–1.65)	1.63 (0.85–3.11)
Moderate	36	50	1.78 (1.17–2.71)	1.72 (1.04–2.87)	44	1.90 (1.14–3.17)	1.15 (0.57–2.33)
Severe	31	65	2.36 (1.54–3.59)	2.01 (1.27–3.19)	48	2.13 (1.26–3.61)	1.65 (0.92–2.96)
≥ 70 years							
No	203	59	1	1	35	1	1
Mild	53	66	1.41 (1.01–1.98)	1.46 (1.02–2.10)	36	1.17 (0.72–1.92)	1.19 (0.68–2.07)
Moderate	54	70	1.40 (1.02–1.93)	1.18 (0.84–1.66)	33	1.23 (0.76–1.98)	0.90 (0.54–1.53)
Severe	47	77	1.50 (1.07–2.10)	1.97 (1.37–2.85)	43	1.38 (0.85–2.24)	1.93 (1.11–3.37)
Female							
No	433	34	1	1	28	1	1
Mild	47	40	1.50 (1.02–2.21)	1.25 (0.82–1.88)	23	0.96 (0.54–1.69)	0.94 (0.50–1.77)
Moderate	53	68	2.71 (1.95–3.78)	1.61 (1.11–2.34)	53	2.31 (1.54–3.47)	1.47 (0.91–2.39)
Severe	47	66	2.75 (1.95–3.87)	1.94 (1.32–2.85)	49	2.01 (1.29–3.13)	1.84 (1.09–3.11)
Male							
No	478	36	1	1	26	1	1
Mild	59	61	2.26 (1.65–3.10)	1.93 (1.37–2.73)	41	1.79 (1.17–2.74)	2.15 (1.34–3.44)
Moderate	54	56	2.29 (1.66–3.15)	1.60 (1.12–2.29)	30	1.80 (1.16–2.79)	1.65 (0.99–2.75)
Severe	39	72	2.68 (1.86–3.86)	2.23 (1.50–3.11)	38	2.02 (1.22–3.50)	2.50 (1.42–4.42)
1979–1988							
No	222	39	1	1	31	1	1
Mild	19	68	2.14 (1.30–3.50)	1.46 (0.82–2.57)	37	1.18 (0.55–2.57)	0.96 (0.39–2.37)
Moderate	19	53	1.79 (1.08–2.96)	0.90 (0.46–1.77)	42	1.61 (0.83–3.10)	0.71 (0.26–1.96)
Severe	8	50	2.06 (1.01–4.21)	1.23 (0.55–2.73)	50	1.80 (0.73–4.44)	1.08 (0.37–3.13)
1989–1998							
No	302	32	1	1	23	1	1
Mild	31	48	2.24 (1.48–3.39)	1.71 (1.10–2.66)	26	1.49 (0.79–2.78)	1.85 (0.94–3.63)
Moderate	33	76	4.02 (2.73–5.91)	1.64 (1.04–2.59)	42	3.03 (1.77–5.18)	1.77 (0.93–3.37)
Severe	24	63	2.46 (1.56–3.88)	2.01 (1.21–3.32)	42	1.84 (0.95–3.53)	2.53 (1.17–5.48)
1999–2008							
No	387	35	1	1	27	1	1
Mild	56	48	1.59 (1.08–2.34)	1.58 (1.04–2.40)	36	1.41 (0.87–2.27)	1.59 (0.94–2.68)
Moderate	55	56	2.15 (1.51–3.05)	1.83 (1.24–2.71)	40	1.92 (1.24–2.96)	2.06 (1.26–3.38)
Severe	54	74	3.03 (2.17–4.25)	2.59 (1.73–3.87)	44	2.26 (1.46–3.49)	2.30 (1.34–3.95)

CI, confidence interval; HR, hazard ratio; N, number. *Analyses adjusted for age, sex, stage at diagnosis, tumor size, depth, grade, surgical margin, radiotherapy, and chemotherapy.

Charlson's Comorbidity Index [3,4,6,23]. This difference might be explained by the different etiologies in the different cancer types, e.g. alcohol and smoking in head and neck cancer, which themselves are associated with comorbidity. Furthermore, since the prevalence of comorbidity increases with age, differences in age at diagnosis between different cancer

types may affect the prevalence of comorbidity. The median age at diagnosis in our study was 59 years, compared to, e.g. 70 years for renal cancer and 72 years for bladder cancer [4,6]. Contrary to with the findings of other studies, the overall prevalence did not increase over time [4,6,23]. This contradiction may be caused by differences in inclusion or

prevalence of diagnoses, since these studies included diagnoses from outpatient visits.

Mortality

Comorbidity significantly impacts survival in various other cancer types such as head and neck, renal, colorectal, and ovarian cancer [3,4,6,23]. Only two studies have, to our knowledge, investigated comorbidity and survival in soft tissue sarcoma [7,8]. The impact of comorbidity on disease-specific survival was investigated in 322 high-grade non-metastatic soft tissue sarcoma patients and 345 patients with tumors located in the extremity and trunk, respectively. Gadgeel et al. assessed comorbidity as a binomial categorical variable (score 0 vs. score 1+), whereas Nakamura et al. assessed comorbidity both as a binomial categorical variable and as a continuous linear variable. Comorbidity was not significant in either of the univariate analyses (Gadgeel et al.: HR = 1.4, $p = 0.41$. Nakamura: 5-year disease-specific survival score 0: 65% vs. score 1–4: 58.9%, $p = 0.58$, and HR = 1.306 pr. 1 point increase in score, $p = 0.12$) and was therefore not analyzed multivariately [7,8]. Contrary to this, we found that comorbidity had a significant independent prognostic impact on disease-specific mortality. The difference in our results might be explained by the different categorization of comorbidity, since our crude analysis of disease-specific mortality showed that moderate and severe comorbidity were statistically significant, while mild was not. Or it can be explained simply by differences in exclusion criteria and sample size.

Patients with comorbidity may be diagnosed earlier, due to a closer contact with the healthcare system, or they may experience a delay in the diagnosis. The latter is supported by our finding that significant more patients with moderate or severe comorbidity had metastases at diagnosis compared to patients with no or mild comorbidity. However, as seen in the adjusted analysis, this difference in stage does not entirely explain the difference in mortality. The treatment of soft tissue sarcoma patients differs according to the disease stage and whereas the treatment of localized disease primarily is surgery, with adjuvant radiotherapy, the treatment of metastatic disease often involves combinations of surgery, radiotherapy, and chemotherapy. The presence of comorbidity might affect the treatment strategy in different ways: the estimated perioperative mortality risk is considered too high, patients might not tolerate chemotherapy, or drugs used to treat comorbid diseases might interact with chemotherapeutic drugs. Whereas the overall proportion of patient treated with surgery was equal regardless of the level of comorbidity, the

aggressiveness of surgery, i.e. surgical margin as well as treatment with radiotherapy and chemotherapy was significantly different. This indicates that patients with comorbidity might not be treated optimally in regard to their soft tissue sarcoma in some cases, resulting in a higher sarcoma-specific mortality, even when adjusting for the treatment. However, patients with comorbidity might experience more complications than patients without comorbidity, resulting in a higher morbidity and mortality. There is therefore a need for increased attention regarding comorbidity, especially in patients with metastatic soft tissue sarcoma in order to improve and optimize the treatment.

Conclusion

The prevalence of comorbidity in soft tissue sarcoma patients is relatively low. The level of comorbidity impacts both overall and disease-specific mortality, and patients with mild, moderate, and severe comorbidity had a significantly increased disease-specific mortality compared to patients without comorbidity, even when adjusting for important prognostic factors including age. Soft tissue sarcoma might not be treated optimally in patients with comorbidity, and improved knowledge and awareness of comorbid diseases is important in order to prevent complications and improve treatment.

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Supplementary material available online

Supplementary Table I