Poor prognostic features among soft tissue sarcoma patients: analysis based on the first sarcoma registry in South Africa

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Citation: Maimin D, Waters R, Kruger N, Bauer HFC, Hilton T. Poor prognostic features among soft tissue sarcoma patients: analysis based on the first sarcoma registry in South Africa. SA Orthop J. 2026;25(1):45-50. http://dx.doi.org/10.17159/2309-8309/2026/v25n1a7

Editor: Prof. Theo le Roux, University of Pretoria, Pretoria, South Africa

Received: January 2025

Accepted: April 2025

Published: March 2026

Funding: No funding was received for this study.

Conflict of interest: The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

Abstract

Background

Soft tissue sarcomas (STS) of the extremities are rare tumours with various prognostic factors. The epidemiology of STS is understudied in South Africa. Here we present the first data on extremity STS from the South African Sarcoma Registry.

Methods

The study comprised a retrospective review of extremity, pelvis and trunk wall STS patients collected from 2019 to 2023 in a prospective South African Sarcoma Registry. One hundred and three STS patients were referred to the orthopaedic oncology unit from 2019 to 2023 and, after exclusion of 14 patients with well-differentiated liposarcomas, data for 89 patients were analysed. To assess survival post-diagnosis, the South African Medical Research Council (SAMRC) National Population Death Registry (Burden of Disease Research Unit) was scrutinised using patient ID numbers. Only patients with ID numbers were utilised for two-year survival curve analysis. To assess factors associated with two-year survival rate, a univariate and multivariate Cox regression analysis was performed.

Results

The median age of the cohort was 49 years; the median tumour size was 11 cm; and metastasis was present at diagnosis in 17% of the cohort. Furthermore, less than half were referred before biopsy or surgery, and 10% were not operated due to metastatic disease at presentation. Overall two-year survival proportion for all patients was 0.70, and for those without metastasis at diagnosis it was 0.80. The two-year survival estimates for patients referred 'untouched' was 0.83, and for those referred with history of prior biopsy or surgery was 0.76. Tumour size was the only factor with a significant impact on two-year survival rates for patients without metastasis at diagnosis ($p < 0.001$).

Conclusion

In our registry, STS patients had more poor prognostic features compared to Scandinavian registry data. Patients tended to present younger, with larger tumours and more frequent metastasis at diagnosis. Generating clinical data through a prospective and consecutive accrual of patients into a registry is paramount for assessment of quality of care and for clinical research.

Level of evidence: 3

Keywords: sarcoma, registry, orthopaedic oncology

Introduction

Soft tissue sarcomas (STS) are a heterogenous group of tumours which can originate from any form of mesenchymal tissue, and are broadly classified by location, as extremity, trunk, intra/retroperitoneal, head and neck, and thoracic.[1,2] Sixty per cent of STS occur in the extremities.[3,4] These tumours are classified by the World Health Organization (WHO) into 11 different groups according to the tissue of origin, and those groups are further subclassified according to biological tumour behaviour as benign, intermediate or aggressive.[1,5]

Epidemiological data is difficult to interpret due to the broad range of clinical manifestations of these tumours and is underreported outside of the developed world. Incidence in the United States of America (USA) is reported at 3.6–4.0 per 100 000 persons.[2,6,7] Significantly higher rates are reported across Europe and the United Kingdom at 5.6 and 7.7 cases per 100 000 persons, respectively.[6,8] The Ibadan (Nigeria) cancer registry reports low rates of STS: 0.4 and 0.8 per 100 000 for females and males, respectively.[9] These differences in reported incidence are due to many factors, including healthcare provision, accurate data accrual and population age distribution. For example, the median age of STS patients is 62, 58 and 47 years in Scandinavia, USA and Nigeria, respectively.[5,9,10]

Epidemiological data on STS is underrepresented in South Africa. Hence, the South African Sarcoma Registry was established

in 2021, and data on STS of the extremities and bone sarcoma patients have been collected retrospectively from 2019 to 2023, and since then prospectively.[11] Here, we present the first data of STS of the extremities, pelvis and trunk wall in patients treated in the Western Cape, South Africa. Our hope is to expand the registry to other parts of South Africa by encouraging specialists to collect data at their respective institutions and incorporate the registry into the greater South African Orthopaedic Registry.

Methods

A retrospective review of data collected for a prospective South African Sarcoma Registry was performed on all STS patients, with tumours located in the extremities and the trunk wall and pelvis, referred to our orthopaedic oncology unit from 2019 to 2023. Local ethical approval was obtained from our Faculty of Health Sciences.

Our local and systemic staging workup consisted of standard blood work, magnetic resonance imaging (MRI) of the entire limb for biopsy planning, as well as a computed tomography (CT) scan of the chest and abdomen. Core biopsy was the preferred method. Open surgical biopsies were only performed if core biopsies did not provide adequate biopsy material for diagnosis. Guidance with ultrasound (US) or CT was performed when necessary. Biopsies for STS in the state hospital were performed as a minor procedure in the outpatient department by an oncology surgeon without image guidance, using local anaesthetic and a 16-gauge core biopsy needle. This is due to resource constraints of available radiology, imaging and theatre time. In private hospitals, biopsies were performed with a radiologist present, using either CT or US guidance to assist the radiologist and oncology surgeon in sample collection. Once excised, all tumours were sent in formalin for histological analysis. Tumours were assessed macroscopically and measured along their longest axis. Microscopic assessment included differentiation, mitotic count, and necrosis, and graded using the French Federation of Cancer Centers Sarcoma Group System.[12] Once biopsy results were made available, the patient was discussed on an individual basis at a multidisciplinary meeting consisting of radiologists, pathologists, oncologists and both orthopaedic and general surgeons. Histology and imaging were presented, and both surgical and oncological plans were formulated and actioned. Follow-up with clinical examination and chest CT or radiographs were planned every three or six months after treatment. Follow-up in this cohort was difficult to achieve and was therefore incomplete.

Registry data were extracted from the dedicated Research Electronic Data Capture (REDCap) registry database into Microsoft Excel. Extracted data included demographics, referral date and referral status, type of biopsy, histological subtype and grade, metastasis at diagnosis, tumour size, and depth, i.e. subcutaneous, deep intra- or extra-compartmental. In addition, referral status pertains to whether the patient had undergone any interventions prior to referral. Treatment variables recorded were type of surgery (local excision or amputation), surgical margins (R0 = marginal or wide, R1 = intralesional), and administration of pre- or postoperative radiotherapy and/or chemotherapy. Simple descriptive statistics were used to characterise the cohort. Data analysis was performed on a subset of the patients, excluding those with well-differentiated (lipoma-like) liposarcomas (grade 1).[13] To assess survival post-diagnosis, the South African Medical Research Council (SAMRC) National Population Death Registry (Burden of Disease Research Unit) was scrutinised using patient ID numbers, and only linked data were utilised for two-year survival curve analysis using the Kaplan-Meier method. In addition, a survival curve analysis was performed to compare patients referred untouched (no prior biopsy or surgery) versus touched (prior core biopsy or open biopsy, surgery). A log-rank test was performed to compare the survival of these patients. A univariate and multivariate Cox regression analysis was performed using SPSS (IBM V29.0) to assess the impact of age, tumour size, grade or location on the two-year survival rate in patients without metastasis at diagnosis.

Results

Table I: Characteristics of 89 STS patients presenting to a sarcoma centre for diagnosis and treatment from 2019 to 2023 and recorded in the South African Sarcoma Registry

Patients, n (%)	89	100
Age years, median (range)	49 (10–90)	
Sex, n (%)		
Female	48	54
Male	41	46
Referral status		
No biopsy or surgery performed	42	47
Core biopsy	29	33
Excision biopsy	14	16
Open biopsy	3	3
Local recurrence after prior surgery	1	1
Tumour grade		
I	21	24
II	18	20
III	40	45
Not graded, e.g.: alveolar sarcoma, mesenchymal chondrosarcoma, etc.	10	11
Major histotypes		
Undifferentiated/unclassified sarcoma (UPS)	16	18
Myxofibrosarcoma	15	17
Liposarcoma	12	13
Synovial sarcoma	12	13
Size of tumour, median (range), cm	11 (1–50)	
Metastasis at diagnosis	15	17
First surgery performed		
Local excision	73	82
Amputation	5	6
Not operated	11	12
Surgical margin		
Marginal	35	39
Intralesional	22	25
Wide	21	24
None	11	12
Oncological treatment		
Radiotherapy	28	31
Chemotherapy	13	15
Radiotherapy and chemotherapy	11	12
None	37	42
Time from referral to treatment*, days: median (range)	43 (5–488)	
Time from diagnosis to treatment*, days: median (range)	37 (0**–420)	

STS: soft tissue sarcoma; *Treatment = surgery or chemotherapy or radiotherapy; ** Operated on the same date as diagnosis

One hundred and three STS patients were referred to the Sarcoma Unit from 2019 to 2023. Seventy patients were treated in state hospitals and 33 in private. After exclusion of 14 patients with well-differentiated liposarcomas, 89 patients remained for data analysis (*Table I*).

The median age was 49 (range: 10–90) years, with half of the presenting patients younger than 50 years of age, and 54% of the cohort were female. Forty-two (47%) patients were referred to a sarcoma centre without previous biopsy or surgery; 29 (33%) were referred after core biopsy; 14 (16%) after excision biopsy; and three (3%) after an open biopsy. Two (2%) patients were referred after local tumour recurrence after having definitive surgery performed elsewhere. Seventy-seven per cent of STS were diagnosed by means of core biopsies, 17% by excision, and 6% by open biopsy. The most common tumour location was the in the lower limb (55%) with 33% and 13% located in the thigh and lower leg, respectively. The shoulder/upper arm was next most common (15%). Thirty-six per cent of lesions were subcutaneous, 20% intramuscular, and 44% extra-compartmental deep. The median tumour size was 11 (1–50) cm. The most common histological subtypes were undifferentiated/unclassified sarcoma (UPS) (18%), myxofibrosarcoma (17%), liposarcoma (13%), and synovial sarcoma (13%). Grading, according to the National Federation of Cancer Centers (FNCLCC) system, revealed 24% low-grade, 20% grade II and 45% grade III tumours. Eleven per cent of the STS were not graded. Metastasis at diagnosis was evident in 15 (17%) patients.

In our study, core biopsies were performed in 78% (69/89) of our patients. Of these core biopsies, the presence of an STS was confirmed after a single biopsy event in 59 cases (85%). It is

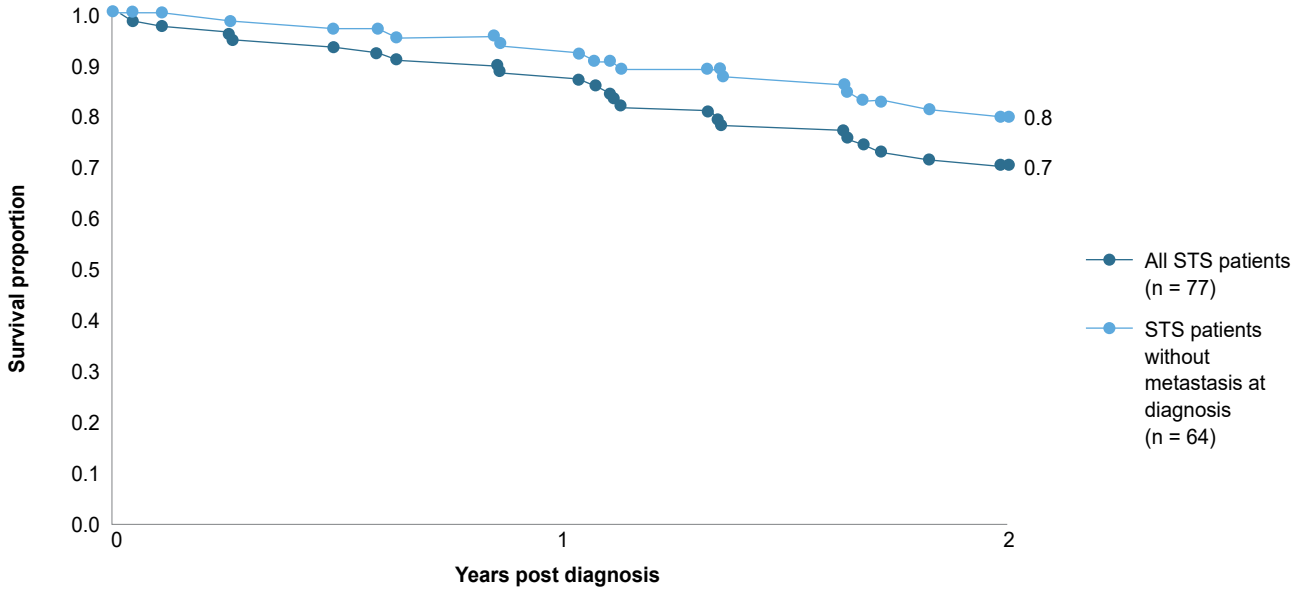

Figure 1. Two-year survival proportions for all patients identified in the Medical Research Council (MRC) Death Registry (n = 77, dark blue line) and for patients without presence of metastasis at diagnosis (n = 64, light blue line)

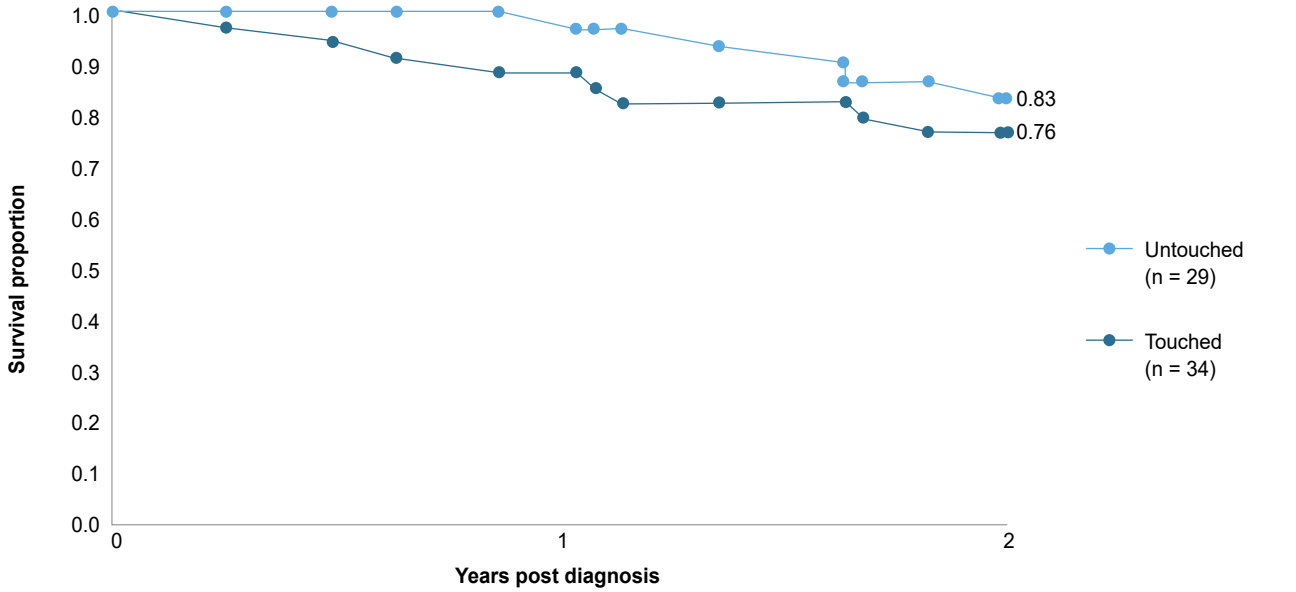

Figure 2. Two-year survival proportions from diagnosis for untouched* vs touched** STS patients without metastasis at diagnosis. Log-rank test (p = 0.482).

* Referral status: no biopsy or surgery performed

** Referral status: core biopsy or excision biopsy

Table II: Multivariate Cox regression analysis of four factors that could impact two-year survival rates of patients without metastasis at diagnosis (n = 64) with available associated death data

Factors	Significance	95.0% CI for Exp(B)	
		Lower	Upper
Age	0.031	1.004	1.093
Size	0.001	1.004	1.018
Grade	0.954	0.000	4.703E + 188
Location	0.103	0.743	25.858

Exp(B) in a multivariate Cox regression is the hazard ratio, representing the multiplicative change in the hazard for a one-unit increase in the predictor, adjusted for all other variables in the model

worth noting that in public hospitals, the rate of correct diagnosis after single biopsy was lower at 82%, compared to 95% success rate seen at the private hospital facilities. This may be due to inappropriate sampling techniques during core biopsies prior to referral to oncology in the public sector or the additional imaging techniques used in the private setting. A success rate of 86% (18/21) was noted if the core biopsy was performed by our unit at our public facility, compared to 79% (19/24) success rate if a biopsy was attempted prior to referral to us.

Local excision was feasible in 82% of the patients, 6% underwent amputation, and 10% of patients were not operated on because of metastatic disease. The surgical margin was R0 (marginal or wide) in 72% and R1 (intralesional) in 28% among the 78 operated patients. The rate of intralesional excisions among patients operated at our unit was 25%. Adjuvant chemotherapy and/or radiotherapy was administered to 58% of the patients.

Median time from referral to start of treatment (surgery or oncological) was 43 (5–488) days and median time from diagnosis to start of treatment was 37 (0–420) days.

Linked data associated with death status were available for 77/89 patients (87%). The overall two-year Kaplan-Meier survival estimate from diagnosis was 0.7. Including only patients without metastases at diagnosis, the two-year survival rate was 0.8 (n = 64) (*Figure 1*). The two-year survival estimates for patients referred 'untouched' was 0.83 and for those referred with history of prior biopsy or surgery, was 0.76 (p = 0.482) (*Figure 2*).

A multivariate Cox regression analysis revealed that size of tumour was significantly associated with mortality within two years for patients without metastasis at diagnosis (p < 0.001) (*Table II*).

Discussion

Here, we report the first data of 89 consecutive STS patients in a South African setting. Compared to European data, patients were younger, with a median age of 49 years, a median tumour size of 11 cm, and metastasis was present in 17% of the cohort at diagnosis.[14] Furthermore, less than half were referred before biopsy or surgery and 10% were not operated due to metastatic disease at presentation. Two-year survival estimate for patients without metastasis at diagnosis was 0.8.

The Western Cape of South Africa is home to over 7.4 million people.[15] The province has only two orthopaedic oncology units providing services to these people. Adding to the burden on these limited services, neither of the Western Cape's two neighbouring provinces, the Northern Cape and the Eastern Cape, have dedicated orthopaedic oncological services. These two neighbouring provinces have a combined population of over 8.5 million people, and definitive surgical and oncological management will usually take place at one of the two orthopaedic oncology services in the Western Cape.[15]

Coupled with this are unique cultural practices that include late presentation after initial visits to traditional healers, delaying of treatment where patients may require time to consult their elders and ancestors, as well as outright refusal of treatment in cases where amputation is proposed.[16,17]

The presented data provides a benchmark for comparison with clinical data from other regions and for assessment of improvement in the care of sarcoma patients. Compared to population-based data from Scandinavia, the tumours were larger, and more patients had metastases at diagnosis, which are the strongest risk factors for poorer outcomes in STS.[17] However, one must be careful with comparisons as the normal age distribution in South Africa is quite different from that of Scandinavia. Follow-up may not be that important as we already know that the outcome in STS is dependent on clinical features at presentation and on treatment.

The incidence of STS increases with age, with peak incidence in the seventh decade reported in European and North American data compared to the fifth decade in this series.[4,5,14,18] Similarly, in other African registries, STS present in younger ages than in Europe and America. In a Ugandan study, the peak incidence was reported in 15–30-year-olds, and 67% of the study cohort was younger than 45 years.[19] The Nigerian registry had 61% of their cohort under the age of 53 years.[9] This is believed to be due to the striking differences in the underlying population age distributions. There is no evidence that STS of the same histotype are inherently different in an African compared to a European/American population.

Open biopsy, once considered the gold standard in the diagnosis of soft tissue lesions, is now largely replaced by core needle biopsies, as open biopsies require dedicated theatre time, and harbours the risk of haematoma, infection and contamination of surrounding tissue with tumour.[3,20] Core needle biopsies have been shown to differentiate benign from malignant tumours in more than 9/10 patients, providing sufficient information to inform treatment.[21-23] It is well established in orthopaedic oncology that not only treatment, but also initial diagnosis should be at a sarcoma centre. In this series less than half of the patients were referred before any diagnostic procedures. This meant delay in treatment, repeat biopsies, unnecessary surgical biopsies and even excisions, so-called 'whoops procedures'.[24] These findings emphasise the importance of referring patients to an established sarcoma centre before any biopsy is performed. In South Africa, this may be difficult to achieve as many of our patients need to travel long distances to reach our facilities, and possibly the knowledge about appropriate sample collection methods and related STS diagnostics may be lacking.

Comparison of histological subtypes among registries is difficult. The age distribution is important as some STS such as synovial sarcoma are more common in the young. Accordingly, 13% of our patients had synovial sarcomas, compared to 6% in the Scandinavian Sarcoma Register with a much older age distribution.[14] The differences in availability of performing extensive immunohistochemical and cytogenetic studies to determine subtype also complicates comparisons. Furthermore, histological classifications are continually evolving. Fibrosarcomas, which were common 30 years ago, hardly exist today.[9,19] Undifferentiated STS were seen in only 4% in the Ugandan series but accounted for

15% in ours and 17% in the Surveillance, Epidemiology, and End Results (SEER) registries.[3-5,10]

The median tumour size in our registry is in keeping with trends from other African series. In the Ibadan registry, tumour size was less than 5 cm in 59 (18%), between 5 cm and 10 cm in 94 (29%), and greater than 10 cm in 173 (53%).[9] Similarly, in Uganda, 100% of the tumours in their series were greater than 5cm on presentation.[19] The Scandinavian registries report an average tumour size of 7 cm, and larger tumours tended to be in patients over 80 years of age.[10] The North American SEER group reports that 60% of their STS were less than 10 cm at excision.[18]

R0 (marginal or wide) resection was confirmed histologically in 72% of our cases. The Scandinavians report R0 margins in 88% of cases over a 25-year period.[25] Other European series report R0 histological margins in 91% of cases.[26] North American and Asian series report R0 margins in 85 and 95% of cases, respectively.[27] Hence, the present results are better than reported previously from other African countries, but not quite on par with European or North American series. This finding is multifactorial such as large tumours, poor referral pathways and fewer subcutaneous lesions. They also point to how major improvements can be made by simply improving referral practices.

Seventeen per cent of our patients had metastatic disease at presentation. Metastasis in STS is identified in approximately 8–13% of patients in international series.[2,3,10,18] Our incidence is better than that reported by the Nigerian registry, which found metastasis to the lungs in 23% of patients, but worse than in Scandinavia where incidence is less than 10%.[14] Metastasis at presentation is the strongest negative prognostic factor and is an important measurement of quality of care. Early referral is critical and may yield smaller tumours and fewer patients presenting with metastatic disease at diagnosis.

Our registry cannot yet report long-term survival rates; however, we report an overall 0.7 two-year survival estimate. This is in contrast to the approximately 0.73 five-year metastasis-free survival reported from the Scandinavian Sarcoma Registry.[14] Overall, the survival rate for STS has been improving over the past 20 years in developed countries.[5,14,18] The SEER registry reports progressively increased five-year survival rates from 47% in the 1999–2005 group to 77% in the 2013–2019 group.[18] This improvement is not due to chemotherapy as such treatment in STS has still been proven to be of limited impact. The poor survival rate reported here confirms the need to improve care of sarcoma patients in South Africa. As in developed countries during the last 50 years, this can be achieved by early referral of patients to sarcoma centres.

The South Africa Sarcoma Registry is in its early stages of data collection and implementation. Hopefully, this report will inspire more sarcoma centres in South Africa to add patients to the registry. The process of finding and recording primary tumour data and acquiring follow-up is time-consuming. A comprehensive knowledge of sarcomas is essential to ensure quality of data. In Sweden, even after almost 40 years, only sarcoma surgeons enter patients into the registry. Follow-up is always difficult to achieve, but especially so in low-resourced environments. However, follow-up is not that important as the outcome is decided by tumour characteristics and treatment. If we can improve referral, then we know that the outcome will also improve. The data presented here can, in this respect, serve as a benchmark for further studies of STS patients in South Africa, and in other developing countries.

Conclusion

STS in our, and in other African settings, tends to present at a younger age, with larger tumours and more frequent metastasis at diagnosis. Histological grade and subtypes are similar across all registries. In conclusion, generating clinical data through a prospective and consecutive accrual of patients into a registry is paramount for assessment of quality of care and for clinical research.

Acknowledgements

We thank Ms Siyasanga Ntshanka for assisting with obtaining patient information to obtain the death data, and the SAMRC Burden of Disease Research unit for providing linked death data.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Prior to commencement of the study, ethical approval was obtained from the University of Cape Town, HREC approval reference number: 757/2024. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed written consent was not obtained from all patients for being included in the study.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

DM: wrote the manuscript
RW: performed the data extraction and analysis outputs, wrote the manuscript
NK: assisted with survival data collection, reviewed the manuscript
HCFB: conceived and designed the registry and analysis, wrote the manuscript, reviewed the manuscript
TH: conceived and designed the registry and analysis, reviewed the manuscript

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