Diplomarbeit

Differential diagnosis TB: Analysis and evaluation of patients with tuberculosis affecting the bones and soft tissues, a retrospective study

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Graz, am 10.03.2022

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 10.03.2022 *Lisa Maria Putzl eh.*

Danksagungen

Ich möchte mich hiermit bei Univ. FÄ Priv.-Doz.in Dr.in med. univ. Dr.in Susanne Scheipl, Univ. FÄ Priv.-Doz.in Dr.in med. univ. Dr.in Ines Vielgut sowie Dr. med. univ. Richard Zettl für die hervorragende Betreuung meiner Arbeit bedanken.

Weiters möchte ich mich noch bei Dr. med. univ. Alexander Indra (mein Ansprechpartner bei der österreichischen Agentur für Gesundheit und Ernährungssicherheit, AGES), Ass.-Prof. Priv.-Doz.in Dr.in med. univ. Tanja Kraus, Dr.in med. univ. Ingrid Thomüller sowie Dr.in med. univ. Ulrike Wittig für die tatkräftige Unterstützung der Datenerhebung bedanken. Ein herzliches Dankeschön gilt auch Dr. med. univ. Thomas Valentin für die Bereitstellung seiner infektiologischen Fachkenntnisse sowie Dr.in Dr.in med. univ. Jasminka Igrec für die radiologische Datenauswertung.

Mit den Daten, die für diese Diplomarbeit gesammelt wurden, wurde auch ein Manuskript (mit dem Titel: „Musculoskeletal tuberculosis revisited: Bone and joint tuberculosis in the Austrian population“) verfasst, das zum Zeitpunkt der Abgabe noch unveröffentlicht ist. Vereinzelt wird auf Daten dieses Manuskript im Text bezuggenommen, wie beispielsweise auf die radiologische Auswertung der extraspinalen Tuberkulosemanifestationen, welche durch Dr.in Igrec erfolgt ist, in Tabelle 4 (Seite 26) bzw. im Absatz „3.2.2.2 Extraspinal TB localisations“ (Seite 28). Diese Bezugnahmen erfolgen mit dem Einverständnis der Urheberinnen Dr.in Igrec, Dr.in Vielgut und Dr.in Scheipl. Ich möchte mich an dieser Stelle bei sämtlichen Co-Autor*innen nochmals für die großartige Zusammenarbeit bedanken.

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List of abbreviations

AGES	-	Austrian Agency for Health and Food Safety
AWMF	-	Association of the Scientific Medical Societies in Germany
DNA	-	Deoxyribonucleic acid
E.G.	-	Exempli gratia
EMB	-	Ethambutol
FFP		Filtering face piece
HIV	-	Human immunodeficiency virus
I.E.	-	Id est
IGRA	-	Interferon gamma release assay
INH	-	Isoniazid
M.	-	Mycobacterium
MDR (-TB)	-	Multidrug-resistant (TB)
MG	-	Milligramm
MRI	-	Magnetic resonance imaging
PCR	-	Polymerase chain reaction
PZA	-	Pyrazinamide
RMP	-	Rifampicin
SOP	-	Standard operating procedure
TB/(TBC)	-	Tuberculosis (german abbreviation)
VS	-	Versus
WHO	-	World Health Organization
XDR (-TB)	-	Extensively drug-resistant (TB)

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Zusammenfassung

Einleitung: Fälle von muskuloskelettaler Tuberkulose (TBC) sind in den vergangenen Jahrzehnten in Österreich zunehmend zur Rarität geworden. Da solche Differentialdiagnosen speziell den jüngeren Kolleg*innen vielfach nur mehr aus Lehrbüchern bekannt sind, dient diese Erhebung dazu, die Differentialdiagnose TBC, und im Speziellen deren extrapulmonale Ausprägungsformen im muskuloskelettalen System wieder in das Bewusstsein der Ärzt*innen zu rufen.

Material und Methoden: Diese retrospektive Studie umfasst: (1) die Untersuchung und Analyse der Daten des nationalen TBC-Registers (1995-2019), (2) die retrospektive Erhebung und Auswertung von Patient*innen, welche in unserer Einrichtung seit Beginn der elektronischen Aufzeichnungen wegen muskuloskelettaler TBC behandelt wurden (2005-2019), und (3) die Evaluierung klinischer Leitlinien für die TBC-Prävention und die Meldung im klinischen Arbeitsumfeld.

Ergebnisse: (1) Zwischen 1995 und 2019 wurde in Österreich bei 23.120 Patient*innen eine TBC diagnostiziert. Bei 307 dieser Personen befiel die TBC primär das muskuloskelettale System (1,33%). (2) Die retrospektive Auswertung lieferte 17 Patient*innen, neun Männer (52,94%) und acht Frauen (47,06%). Sämtliche Patient*innen mit Migrationshintergrund (n = 8; 47,06%) waren zum Zeitpunkt der Diagnose jünger als 40 Jahre, während alle gebürtigen Österreicher*innen (n = 9; 52,94%) älter als 60 Jahre waren. Zehn von 17 Patient*innen (58,82%) litten an einer spinalen Form der muskuloskelettalen TBC. Die häufigsten Symptome waren septische oder entzündliche Erscheinungsbilder (41,18%), neurologische Defizite (29,41%) oder der Verdacht auf einen neoplastischen Prozess (29,41%). Im Median wurde die TBC am 14. Tag (mit einer Spanne von 7-405 Tagen) nach der Erstvorstellung diagnostiziert. Sechs Patient*innen erhielten eine rein konservative Behandlung (35,29%), während die übrigen elf Patient*innen (64,71%) zusätzlich operiert wurden.

Diskussion: Um sekundäre Komplikationen zu vermeiden, müssen TBC-Patient*innen so früh wie möglich eine angemessene medikamentöse Therapie erhalten. Daher ist es wichtig, bei atypischen Infektionsereignissen am Bewegungsapparat differentialdiagnostisch an eine TBC zu denken.

Abstract

Introduction: Cases of musculoskeletal tuberculosis (TB) have become increasingly rare in the Austrian population. Younger physicians often only learn about these cases from textbooks. Therefore, this study aims to make doctors aware again of the differential diagnosis of tuberculosis, and in particular of its extrapulmonary form affecting the musculoskeletal system.

Material and Methods: This retrospective study consists of: (1) an enquiry and analysis of the national TB registry data (1995-2019), (2) the retrospective assessment of patients treated with musculoskeletal TB at our institution since the initiation of electronic records (2005-2019), and (3) the evaluation of clinical guidelines for TB prevention and reporting in a clinical setting.

Results: (1) In Austria, a total of 23,120 patients were diagnosed with TB between 1995 and 2019. Amongst these, 307 had a principal manifestation of musculoskeletal TB (1.33%). (2) This retrospective study includes 17 participants, nine men (52.94%) and eight women (47.06%). Patients with a migration background (n = 8; 47.06%) were diagnosed under the age of 40 (with a range from 18-39 years) whereas all native Austrians (n = 9; 52.94%) were diagnosed over the age of 60 (with a range from 63-92 years). Ten out of 17 patients (58.82%) presented with a spinal form of musculoskeletal TB. The most frequent causes for the presentation were septic or inflammatory conditions (41.18%), neurological deficits (29.41%), or suspected neoplastic processes (29.41%). At the median, we initiated TB-specific diagnostic procedures on the 14th day (with a range from 7-405 days) after initial presentation. Six patients received a purely conservative treatment (35.29%), whereas the remaining eleven patients (64.71%) additionally underwent surgery.

Discussion: Timely initiation of drug therapy can prevent secondary TB complications. Therefore, physicians should consider TB as a potential differential diagnosis in case of atypical infectious events in the musculoskeletal system.

1 Introduction

1.1 TB disease agent and his discovery

Tuberculosis (TB) is an infectious disease caused by disease agents summarised as Mycobacterium tuberculosis complex. This summarised disease agents group includes different types of mycobacteria, such as M. tuberculosis, M. africanum, M. bovis, M. caprae, M. pinnipedii, and M. microti. (1)

A study suggests that the causative agent of TB might be at least 3 million years old. In Africa, early hominids might have already been affected by a progenitor of Mycobacterium tuberculosis. (1)

TB is caused by slow-growing bacteria species. The most common disease agent is Mycobacterium tuberculosis (figure 1). Because of his slow division time, this bacterial species has a generation time of 15 to 20 hours. (2) Mycobacterium tuberculosis is a tubercle bacillus, which cannot be stained by Gram´s method. The cell wall of this bacterium has a high portion of lipid content. Due to the mycolic acids in the cell wall, this disease agent is acid-proof. (3)

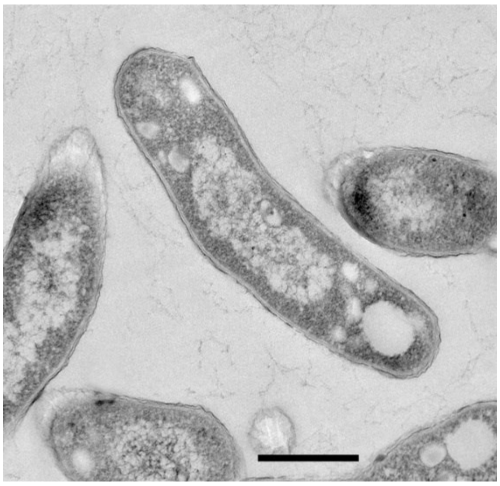


Figure 1. "Mycobacterium tuberculosis" with kind permission of the Robert Koch Institute. Available at: https://www.rki.de/DE/Content/Infekt/NRZ/EM/Aufnahmen/EM_Tab_Mycobacterium_tuberculosis.html. Last accessed 02/20, 2022.

In 1865 a French Physician called Jean-Antoine Villemin speculated based on his research that TB must be an infectious disease. (4) But the cause of TB disease remained further unknown. In the spring of 1882, Dr Robert Koch (1843-1910) successfully isolated the agent of TB disease, a tubercle bacillus. A true milestone in the history of understanding tuberculosis took place on the 24th March of 1882 in

Berlin, as Dr Koch presented his newest research results “Die Ätiologie der Tuberkulose” to the Physiological Society, which earned him the Nobel Prize of Medicine in 1905. (5,6)

1.2 Global epidemiology

According to a World Health Organization (WHO) estimation, about 10 million people fell sick with tuberculosis in 2019. Globally, TB is still one of the top 10 causes of death. It is the leading cause of death amongst single infectious diseases with 1.4 million deaths in 2019. Furthermore, 88% of TB patients in 2019 were adults. Still, 86% of TB cases in 2019 occurred in only 30 TB high-burden countries. Number one of the TB high-burden countries in 2019 was India, with 26% of TB patients, followed by Indonesia (8.5%) and China (8.4%). (7)

According to the WHO, the top two regions with the highest incidence rate of TB cases in 2019 were Africa with 226 TB cases (with an uncertainty interval of 201-252) per 100,000 inhabitants, followed by South-East Asia with 217 TB cases (with an uncertainty interval of 173-266) per 100,000 inhabitants (figure 2). Both countries are above the global average of 130 TB cases (with an uncertainty interval of 116-143) per 100,000 inhabitants. The lowest burden WHO region is Europe with 26 (with an uncertainty interval of 23-30) TB cases per 100,000 inhabitants. (7)

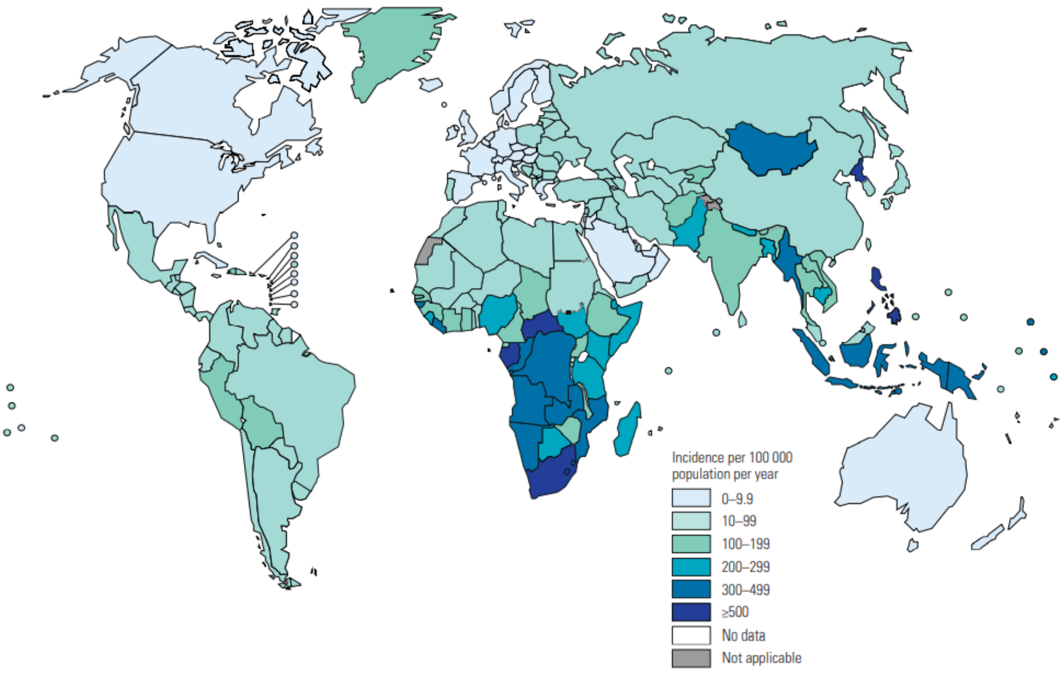


Figure 2. “Estimated TB incidence rates, 2019” with kind permission of the WHO from the Global tuberculosis report 2020 (page 35, figure 4.4). Available at: https://www.who.int/publications/i/item/9789240013131. Last accessed 02/20, 2022.

1.3 The End TB Strategy

The *End TB Strategy* is a project initiated by the World Health Organization (WHO) to reduce the global burden of the TB disease. There are three milestone-periods according to the project: The first period ended in 2020, the second period will end in 2025, and third period will end in 2030. The milestones of the *End TB Strategy* were accepted by all WHO Member States in 2014. One of the key milestones was an 80% reduction of the TB incidence rates by 2030. Another aim was to reduce 90% of the deaths caused by TB until 2030. The comparative values for both aims were the global incidence rate with 142 TB cases per 100,000 people and a death rate of 1.8 million people in 2015. Furthermore, no patient with TB should face disastrous medical costs by 2020. (7,8)

By the end of 2020, the first milestone-period according to the *End TB Strategy* has already been accomplished. In 2020, the incidence of TB was supposed to be reduced by 20%, and the TB death rates should have been reduced by 35%. Unfortunately, reality showed a slightly different picture (figure 3 and 4): Although the overall TB-incidence rate showed a downward trend, its reduction was only 9% compared to 2015. However, a positive effect was that 78 countries (including seven TB high-burden countries) reached the 2020 milestone by reducing their incidence rates by at least 20%. Furthermore, two more WHO regions almost accomplished the 2020 milestone goal; these were Europe with an incidence reduction of 19% and Africa with a reduction of 16%. According to the WHO, only America showed a slight increase in its incidence rate because of an upward trend in Brazil. (7)

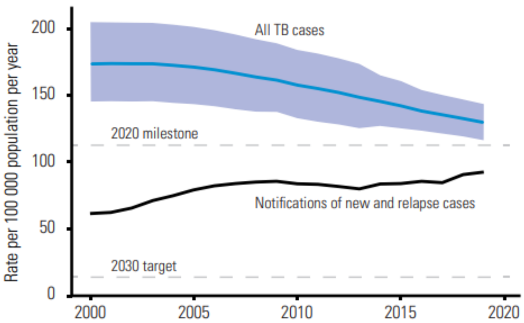


Figure 3. “Global trend in the estimated TB incidence, 2000-2019” with kind permission of the WHO from the Global tuberculosis report 2020 (page 7, figure 2.1). Available at: https://www.who.int/publications/i/item/9789240013131. Last accessed 02/20, 2022.

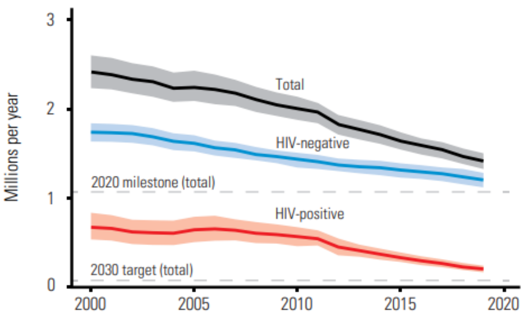


Figure 4. "Global trend in the estimated number of TB deaths, 2000-2019” with kind permission of the WHO from the Global tuberculosis report 2020 (page 8, figure 2.4). Available at: https://www.who.int/publications/i/item/9789240013131. Last accessed 02/20, 2022.

Moreover, the absolute numbers of TB deaths could not be as stringently reduced as aimed for (35%). TB death rates declined by only about 14% worldwide. However, the WHO region Europe almost accomplished the 2020 goal with a 31% reduction. Nevertheless, 46 other countries (including seven TB high-burden countries) are on a promising way to reach the 35% reduction. However, the third goal of the *TB End Strategy* could not be accomplished by 2020, as in 2019, 49% of TB patients still had to face disastrous medical costs for their treatment. (7)

1.4 Transmission and risk factors

Mycobacterium tuberculosis is usually transmitted via aerosols. Whenever contagious lung TB patients speak, spit, sing, cough, or sneeze, contagious aerosols are released. (9) In addition, there are other transmission paths, e.g., via the skin or the placenta. However, the latter transmission paths are very uncommon and epidemiologically irrelevant. (10)

1.4.1 Endogenous risk factors

Only about 10% of people infected with Mycobacterium tuberculosis are estimated to develop an active TB disease. A variety of endogenous factors play a role in developing an active TB infection. The most important endogenous risk factor is a simultaneous HIV co-infection, as this causes a weakness of the immune system. What is more, HIV is endemic particularly in underdeveloped countries that show high TB prevalence rates. Another risk factor is the posttransplant-period after an organ transplantation due to a drug-induced immunosuppression. Further important risk factors are, e.g., a chronic renal insufficiency, haemodialysis, a jejunoileal bypass, or intravenous drug abuse. (10)

1.4.2 Exogenous risk factors

Transmission of tuberculosis is influenced by various exogenous factors. For instance, the duration and intensity of a person´s contact with contagious patients determine the risk for transmitting the disease. Another important factor is the infectivity of TB patients. For example, a patient with cavernous lung TB is more contagious than a person without caverns. These patients will most likely be sputum-smear positive. In those cases, the sputum of the patient contains strains of Mycobacterium tuberculosis that can infect other people. Apart from the infectivity of TB patients, also the virulence of Mycobacterium tuberculosis is an important determining factor for developing tuberculosis. Furthermore, environmental factors support the spread of the infection. For example, a contagious patient who is in a small, crowded, non-ventilated room is more likely to spread the disease than a contagious but isolated patient. (10)

1.5 Pathogenesis

If a person inhales Mycobacterium tuberculosis, macrophages will subsequently get in contact with these germs in the lungs. However, the thick cell wall and the inhibition of intracellular defence mechanisms by the bacterium help Mycobacterium tuberculosis to withstand an extinction by the host´s immune system. Thus, after a short period of time, the primarily affected macrophages perish while trying in vain to kill these bacteria. Consequently, other dendritic cells and macrophages are attracted by the released tubercle bacilli. These immune cells release pro-inflammatory substances to attract even more immune support to the site. Within ten to 14 days after the primary infection, a local focus of inflammation, also known as “Ghon focus”, emerges. Additionally, some bacteria get carried off and cause an immune response in the hilar lymph nodes of the lungs. The responding lymph nodes and the local focus of inflammation form the so-called “Ghon´s complex”. After six to 14 weeks, the immune system forms the characteristic granulomas in an attempt to contain the spread of the tuberculosis bacteria. Furthermore, a tuberculin allergy develops because of specific antigen reactions between the bacteria and specific T-cells. In 90% of primary TB infections, the Ghon´s complex subsequently calcifies, and a scar forms if a host´s immune system successfully manages to contain the bacterial spread. In these cases, no signs of an active TB disease appear. However, viable strains of Mycobacterium tuberculosis may survive in the scars and can thus lead to a post-primary TB disease. (3)

1.5.1 Mycobacterium tuberculosis´ methods of evading a host´s immune system

Mycobacterium tuberculosis has developed two key mechanisms of escaping a host´s immune system. First, Mycobacterium tuberculosis hides potential antigens behind lipids of its own thick cell wall. On the other hand, immune evasion is caused by suppressing an intracellular process. If macrophages detect the tuberculosis bacteria, they incorporate the bacteria via phagocytosis. However, by interrupting the intracellular signal chain, this bacterial species manages to prevent a phagosome´s maturation into a phagolysosome and thus the bacterial extinction by the host´s immune system. Therefore, to prevent the further spread of these pathogens, the immune system encapsulates the affected macrophages into granulomas. Subsequently, Mycobacterium tuberculosis reduces its metabolism and stops its cellular division. However, if the environmental factors become more advantageous for the bacteria, they will reverse their dormant state and induce an active TB infection. (2)

1.6 Clinical stages

Tuberculosis infections can be categorised into latent tubercular infections and active TB. In both cases, the affected person had been in contact with Mycobacterium tuberculosis. A person suffering from a latent infection shows no signs of TB and is not contagious. However, people with latent tubercular infections carry viable but dormant Mycobacterium tuberculosis strains in their bodies. If their immune system is subsequently weakened, those viable bacterial strains will leave their dormant states and induce an active TB infection. (11)

There are two ways of developing active TB (figure 5): First, active tuberculosis can arise immediately after an individual´s first contact with Mycobacterium tuberculosis. This form is referred to as “primary progressive TB”. Particularly children and immunocompromised adults are affected by this primary progressive form of active TB. As these primary forms do not induce cavern formation, these patients are often not highly contagious. (10)

There are several aggressive variants of primary TB which occur in patients with a hampered or not yet fully developed immune system. One of these variants is an aggressively progressive primary TB of the lungs, which mostly occurs in children and young adults. Another form is the so-called “miliary TB”, which is often seen in immunocompromised patients who frequently experience an early haematogenous and lymphogenic spread. They will develop multiple small granulomas throughout their bodies as a sign of a weak immune reaction against the invading bacteria. Landouzy septicaemia occurs if Mycobacterium tuberculosis spreads unopposedly in a very immunocompromised human body who´s immune system is not able to encapsulate the bacteria at all. Finally, primary tuberculous meningitis is seen as a special variant of TB, which usually affects toddlers. (3)

Second, active TB can present itself as so-called “post-primary TB”. This form occurs if the tuberculosis bacteria are contained by a host´s immune system for a certain period after the primary infection had taken place. Of note, half of the patients suffering from post-primary TB develop an active disease within 18 months after primary infection. In post-primary progressive TB patients, the immune system forms the characteristic granulomas in an attempt to contain the spread of the tuberculosis bacteria. Due to the frequent formation of caverns, the infectivity of post-primary TB patients is comparatively higher than the infectivity of patients with primary TB. (3,10)

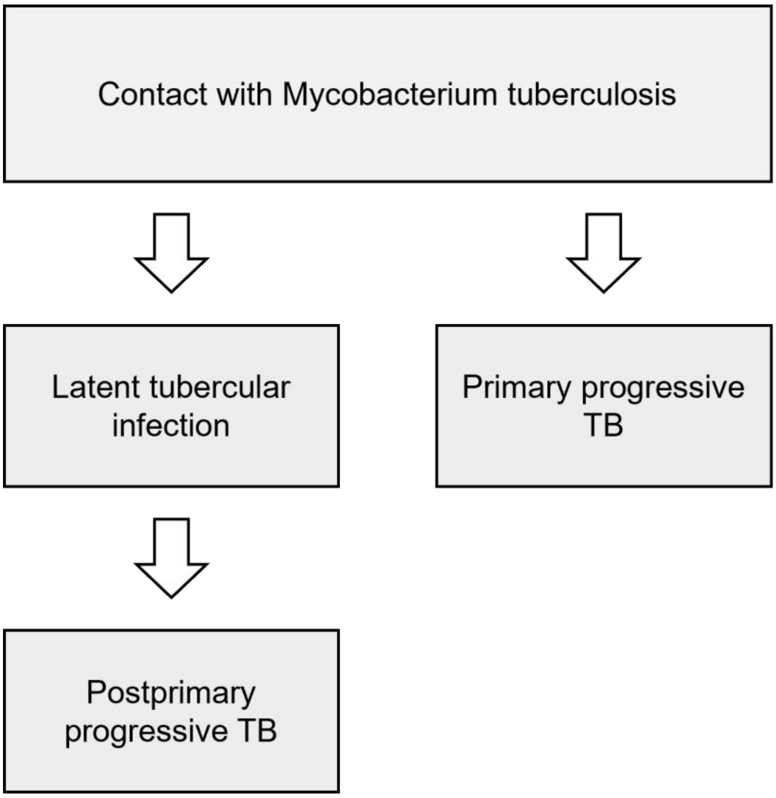


Figure 5. Clinical stages of TB.

1.7 Signs and symptoms

Signs and symptoms largely depend on the clinical stage of TB. For example, a patient with a latent TB infection does not show any infection signs. Additionally, most symptoms of TB are unspecific, such as weakness, fatigue, loss of appetite, weight loss, chills, fever, or night sweats. (12)

Furthermore, infection signs depend on the site of infection. In this context, it is important to be aware that TB can manifest itself in various anatomic sites. Basically, two types of TB disease can be distinguished: pulmonary and extrapulmonary TB. In about 80% of manifest TB, the primarily affected organs are the lungs. The common signs of lung TB are long lasting coughs with or without the release of sputum (which is in rare cases mixed with blood), as well as chest pain, and a shortness of breath. (12)

Extrapulmonary TB includes all other possible locations of TB apart from the lungs. Many cases of extrapulmonary TB have been reported in young children and immunocompromised patients. The most common locations are organs with a high blood supply, such as the adrenal glands, the central nervous system, the bones and joints, as well as the kidneys, the pericardium and abdomen, or – due to a lymphogenic bacterial spread – the lymph nodes. (13)

In the United States of America, for instance, in ten percent of all extrapulmonary TB cases, the symptomatic infected sites are the bones and joints. An infection of the bones is caused by a haematogenous or lymphogenic bacterial spread. A haematogenous infection occurs if the bacteria enter the human bloodstream. Subsequently, particularly bones that are well supplied with blood, e.g., the axial skeleton, are affected. (10) Thereof, spinal involvement also known as "Pott's disease" is the most common form of musculoskeletal TB. Other manifestations such as peripheral joints, skull, or ribs are less common. (14) As the disease progresses, destruction of the bone and surrounding joints may occur, and abscess formations with spread to the surrounding soft tissue, which may present as a mass, are possible. (10)

1.8 Diagnostic tools

Due to a lack of specific signs, tuberculosis is not always easy to diagnose. Therefore, it is particularly important for physicians to keep it in mind as a differential diagnosis. Specific information in a patient´s medical history can help with the diagnosis. To explore a potential differential diagnosis of TB, a patient should always be asked three questions: First, whether he/she had been in known contact with TB patients? Second, if he/she had been traveling to places with high TB rates, like Africa or South-East Asia? Third, whether the patient had been diagnosed with tuberculosis before? Furthermore, symptoms such as general signs of illness and increased inflammation levels indicate an infectious event. (7,11) However, clinical symptoms and radiographic imaging are not sufficient for a diagnosis. To reliably diagnose TB, the molecular biological pathogen detection is necessary. Today´s diagnostic "gold standard" is a culture verification of Mycobacterium tuberculosis in the affected tissue. (3,7,11)

1.8.1 Immunological tests

There are two common immunological screening tools in the diagnosis of TB: First, the Tuberculin skin test, also known as “Mendel–Mantoux test”. For the Tuberculin skin test, a small portion of Mycobacterium tuberculosis will be injected into the patient´s skin. If the patient is infected with TB, a swelling and reddening will occur around the puncture mark in the skin. This reaction is due to a type four allergic reaction, also known as delayed-type hypersensitivity. Thus, this test will only be positive if a host´s immune system has previously been exposed to TB. However, a positive Tuberculin skin test does not necessarily prove a clinically relevant TB infection, as this test can also be positive if a patient´s immune system had been in subclinical contact with Mycobacterium tuberculosis, environmental mycobacteria, or if a patient had previously received a Bacillus Calmette-Guérin vaccination shot. (3) Bacillus Calmette-Guérin can be used as a tuberculosis vaccine to prevent severe forms of the disease, especially in children. (15) The second screening tool is the interferon gamma release assay (IGRA), also known as “QuantiFERON-TB Gold test”. This blood test is more specific in detecting a florid TB infection compared to the Tuberculin skin test. (3)

1.8.2 Pathogen detection

Confirmation of TB diagnosis requires the detection of the pathogen (Mycobacterium tuberculosis). Methods for bacterial detection include the microscopic examination of infected tissue (e.g., after sputum smear microscopy after Ziehl-Neelsen staining), culture-based methods, or molecular tests for detection of bacterial DNA (e.g., nucleic acid amplification tests). (7) All of these methods require tissue samples containing Mycobacterium tuberculosis, for instance sputum, a tissue biopsy, or pus. Today´s diagnostic "gold standard" is a culture verification of Mycobacterium tuberculosis. However, as these bacteria are slow growing, this verification takes up to eight weeks. (2,3) In case a fast diagnosis is clinically relevant, a combination of microscopic examination for pathogen detection and rapid diagnostic tests, e.g., a Mycobacterium tuberculosis-polymerase chain reaction (PCR) test, should be used. (16) The result of the Mycobacterium tuberculosis-PCR examination can be available after only one to two days. In this context, however, it is critical for the interpretation of the results that PCR tests detect the genetic material of Mycobacterium tuberculosis in the test material but cannot distinguish between dead and living bacteria. (17)

1.9 Treatment

If the human immune system cannot stop Mycobacterium tuberculosis from multiplying, people fall sick. In that case, people need drugs to fight their disease. As pulmonary TB is the prevailing form of TB (80%), the subsequent standard treatment regimen will be explained based on the treatment protocol of TB affecting the lungs. (12)

According to guidelines of the Association of the Scientific Medical Societies in Germany (AWMF) for TB affecting adults, people are treated with four antibiotics in the initial phase. Initially, TB patients are supposed to take a combination of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) for two months. Patients need to swallow INH, RMP, and PZA half an hour before breakfast, ideally on an empty stomach. EMB can be taken independently from the meals. After two months, the initial phase ends. In the continuity phase, patients must continue with INH and RMP. According to the standard therapy scheme, TB drugs need to be applied for at least six months in total (table 1). However, there are exceptional cases in which TB drugs can and must be continued for a longer interval. (18)

TB manifestation	**Initial phase (INH + RMP + PZA +EMB)**	**Continuity phase (INH + RMP)**
Lung TB	Two months	**Four** months
Bone and joint TB	Two months	**Seven** months

Table 1. Standard treatment regimen for lung versus bone and joint TB.

For example, patients with bone and joint TB should be on antibiotic treatment for at least nine months (table 1). The initial treatment phase stays the same. However, the continuity phase lasts for seven months instead of four. In exceptional cases, anti-TB drugs need to be continued for even longer. Additionally, patients with neurological deficits, abscess formations or impending fractures of the infected bones will require surgical intervention. (18)

1.9.1 Treatment of drug resistant tuberculosis

According to the AWMF guidelines, patients displaying resistance or intolerance against a single TB drug should receive alternative medications. Additionally, prolongation of the treatment duration is required, and the resistant drug is replaced by fluoroquinolones. Multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) TB cases are more difficult to treat. The treatment of these patients should preferably be conducted in specialised clinics. It usually requires a multi-stage process to identify the best individual therapeutic regimen for each MDR/XDR-TB patient. Initially, a precise resistance testing needs to be performed for diagnostic purposes. In this context, molecular findings need to be confirmed by culture results. Subsequently, at least four different, effective anti-TB drugs must be identified and combined for a successful treatment of MDR-TB patients, and five for patients suffering from XDR-TB. (18)

1.9.2 Chemoprophylaxis and chemoprevention

In case of unprotected contact with contagious TB patients, vulnerable people, for example, immunocompromised adults or children younger than five years, should receive chemoprophylaxis to prevent TB infection. As laboratory parameters, such as Tuberculin skin test and IGRA, do not respond immediately after contact with an infectious TB patient, an early stage of infection can be difficult to prove. Therefore, chemoprophylaxis should start for vulnerable people as soon as possible after a potential transmission of TB, even without proof of infection or immune response. INH 300 mg is immediately given once daily for eight weeks. Then, after eight weeks, a Tuberculin skin test or IGRA test is required. If these parameters are negative, the treatment stops. In the case of a positive test result, the therapy needs to be continued. Once any organ manifestations are ruled out, the latent tubercular infection needs to be treated with chemoprevention. (18)

The concept of chemoprevention aims to prevent the activation of dormant Mycobacterium tuberculosis germs via systemic therapy in who have been demonstrably infected with TB but do not (yet) show clinical manifestations. Particularly risk groups require a chemopreventive therapy once they show a positive Tuberculin skin test or IGRA. To these risk groups belong, for example, HIV positive people, immunocompromised patients, or people with malignant diseases. There are different treatment regimens for chemoprevention. However, the best evidence exists for INH over a nine-month period, or the combination of RMP and INH over three months. (18)

1.10 Drug resistance

In cases of drug-resistant TB, the standard therapy scheme cannot be applied, so that a second-line regimen is required. (7)

There are different forms of drug resistance in TB. In rifampicin-resistant TB, for instance, mycobacteria have become resistant to rifampicin, which is one of the most powerful first-line drugs. In multidrug-resistant TB (MDR-TB), patients display resistance against at least two potent first-line drugs (isoniazid and rifampicin). Extensively drug-resistant TB (XDR-TB) is a severe form of drug-resistant TB. It exerts resistance against two potent first-line drugs (e.g., isoniazid and rifampicin) and to fluoroquinolones. Additionally, XDR-TB does not respond to at least one of the three injectable second-line drugs (capreomycin, kanamycin, and amikacin). (19)

According to the WHO, there was a 10% increase of MDR-/rifampicin-resistant TB worldwide in 2019 compared to the previous year. Only 57% of MDR-/rifampicin-resistant TB patients were treated successfully. (7)

Globally speaking, the last few years saw a rising trend of rifampicin-resistant TB cases, according to the latest data. In 2019, a total number of 206,030 TB patients with MDR-/rifampicin-resistant TB was reported. In Europe, about 23% of TB patients showed multidrug or rifampicin resistance. The highest burden with 42% of multidrug and rifampicin-resistance was observed in South-East Asia. Additional to the MDR-/rifampicin-resistant TB cases, 12,350 patients with extensively drug-resistant TB infections were listed. In total, 69% of these XDR-TB cases were recorded in the WHO Region Europe. (7)

1.11 Vaccination

An effective vaccine would most likely help to prevent the spread of tuberculosis. Unfortunately, the commonly known Bacillus Calmette-Guérin vaccine barely prevents the infection in adults. However, this vaccine protects infants and young children from severe forms of TB infection such as miliary TB or tuberculous meningitis. Thus, the Bacillus Calmette-Guérin vaccine is still in use in countries with high TB incidence and prevalence rates to protect infants and children. Due to the low incidence rates of TB and comparatively high side effect rates of Bacillus Calmette-Guérin vaccinations, these vaccines are not routinely recommended in Austria anymore. (15,20)

1.12 Musculoskeletal tuberculosis

This study aims to summarise the current knowledge on tuberculosis and to recall this disease as a potential differential diagnosis, particularly for bone and joint infections or neoplasms, to Austrian general physicians and orthopaedic surgeons. To do so, the numbers of recorded Austrian TB infections were analysed, dating back to 1995. We also analysed the subgroup of TB infections registered in the Austrian province of Styria, in which our hospital forms the state hospital. In addition, this study retrospectively analyses a case series of musculoskeletal TB patients who were diagnosed and/or treated at the Styrian state and university hospital, the Medical University of Graz, since the establishment of an electronic medical recording system in 2005 (2005-2019). This study furthermore includes a compact summary of a guideline-based assessment, treatment, and prevention of this disease, that has become comparatively rare in developed countries such as Austria.

2 Material and Methods

This study is based on literature research and a retrospective data evaluation. Prior to the start of our study, a positive vote from the Ethics Commission of the Medical University of Graz was obtained (Ethics Commission number: 32-148 ex 19/20).

2.1 Data collection

This retrospective study consists of three parts: 1) An enquiry and analysis of national TB registry data, 2) the retrospective assessment of patients diagnosed and/or treated with musculoskeletal TB at our institution, and 3) the evaluation of clinical guidelines for TB prevention and reporting in a clinical setting which is supposed to result in a standard operating procedure (SOP) for the medical staff at our institution.

2.1.1 National TB registry

First, we analysed the newly reported TB infections of Austria with a special focus on the Austrian county of Styria, as our hospital is located in the latter. For this reason, an inquiry was submitted to the national TB registry, which is hosted by the Austrian Agency for Health and Food Safety (AGES; www.ages.at). Apart from disease numbers, the AGES also documents the organs which were primarily affected by TB at first diagnosis. According to the WHO classification, they distinguish between pulmonary (e.g. lungs) and extrapulmonary manifestations of TB. Amongst extrapulmonary manifestations, various organ sites (e.g. intra- and extrathoracic lymph nodes and others more) are listed. We retrieved this information from the national registry and evaluated the organ affections throughout the period investigated herein (1995-2019). Furthermore, we calculated the incidence rates of TB from 1995 to 2019 using the TB figures provided by AGES and the annual population figures according to Statistics Austria (www.statistik.at). To calculate the annual incidence rates, we used the following formula: Incidence rate = TB cases / (Austrian population / 100,000), also see supplement 3.

2.1.2 Retrospective evaluation of patients with musculoskeletal TB from our institution

In the second part of our study, we retrospectively evaluated all patients who were diagnosed or treated with musculoskeletal TB at the Department of Orthopaedics and Trauma and the former Division of Paediatric Orthopaedics and the Department of Paediatric and Adolescent Surgery (which has become part of the Dept. of Orthopaedics and Trauma in 2020) at the Medical University of Graz since the beginning of electronic recordings. We searched our hospital´s electronic register for the term “tuberculosis” in any context (i.e., diagnosis, treatment, and others more).

2.1.2.1 Patients´selection

This search yielded a total number of 140 patients (80 males and 60 females) who had been diagnosed or treated with tuberculosis at the Department of Orthopaedics and Trauma or the former Division of Paediatric Orthopaedics at the Medical University of Graz. After reviewing these patients´ medical histories, a total of 39 patients (18 males and 21 females) presented with a diagnosis of TB affecting the musculoskeletal system. Subsequently, we excluded 20 patients (7 males and 13 females), as their TB disease was not confirmed by standard methodology (histology, molecular biology, or culture). Two more male patients were excluded because their disease diagnosis and treatment dated back before the initiation of electronic recordings at our hospital (2005). Finally, we ended up with 17 patients (9 males and 8 females) who suffered from histologically, molecularly, or culture-based confirmed tuberculosis affecting their bones or soft tissues and who were further studied as part of our case series (figure 6).

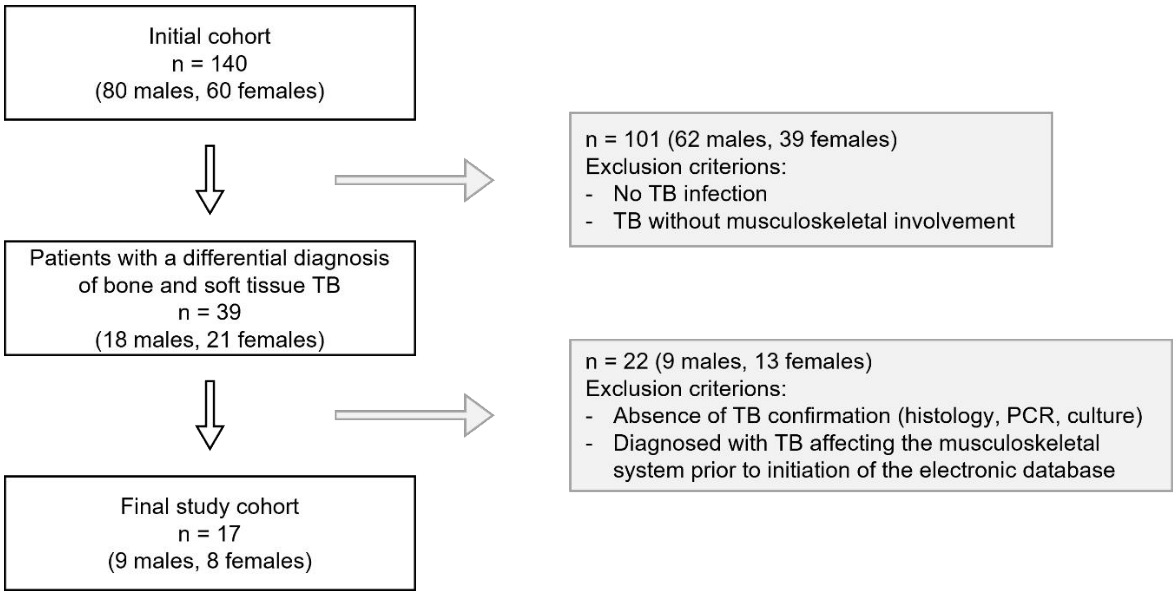


Figure 6. Flow chart illustrating our patients´ selection criteria.

2.1.3 Evaluation of current guidelines for TB prevention and reporting

Based on a literature research we retrieved current guidelines regarding the correct prevention and reporting of TB as far as medical staff is concerned. We furthermore reviewed in-house guidelines and guidelines provided by the national agency in charge (AGES). Subsequently, we discussed these guidelines with our infectious disease specialists of the Section of Infectiology, which is part of the Department of Internal Medicine at the Medical University of Graz and created a SOP together with them in order to allow a protection of medical staff in dealing with cases of suspected TB, as well as proper reporting of this disease to the Austrian health authorities.

3 Results

3.1 Newly reported TB infections

The enquiry at the national TB registry yielded the following numbers of TB infections in Austria (3.1.1.) and the Austrian county of Styria (3.1.2.). The following figures (figure 7-12) and tables (table 2a-3c) are based on data provided by the AGES with kind permission to use them in this thesis.

3.1.1 Austria

According to the AGES, a total number of 23,120 patients were diagnosed with TB between 1995 and 2019 in Austria. Except for three years (2004, 2013, and 2016), a continuous downward trend has been recorded since 1995 (figure 7): in 1995, a total number of 1,633 newly reported cases were documented. Since then, the rate of infected people fell, until there were only 474 documented cases in 2019, i.e. 70.97% fewer infections compared to 1995. This results in an incidence rate of 20.55 per 100.000 people in 1995, compared to an incidence rate of 5.34 per 100.000 people in 2019. Detailed TB infection numbers and incidence rates for each year are given in supplement S1 and S3.

As stated above, there were three years in which this downward trend was reversed: 2004, 2013, and 2016. The latest increase of infected people was seen in 2016 with a total number of 634 newly registered patients. Since then, the number of newly registered TB cases dropped again by 25.24% until it reached a total number of 474 newly infected people in 2019. This was the lowest recorded level ever. Compared to 2018, TB rates dropped by 1.66%, which means that eight fewer cases were recorded in 2019 compared to the previous year.

Overall, as shown in figure 8, most patients were diagnosed with pulmonary TB (n = 18.436; 79.74%). A total of 3,906 patients (16.89%) presented with extrapulmonary TB. The organ involvements are listed in tables 2a-2c**.** Amongst extrapulmonary sites that were frequently affected were extrathoracic lymph nodes and the pleura with 1,448 and 858 reported cases overall, respectively. In contrast, the rarest localisation was the central nervous system including the meninges (n = 98). Disseminated TB was seen in 88 patients.

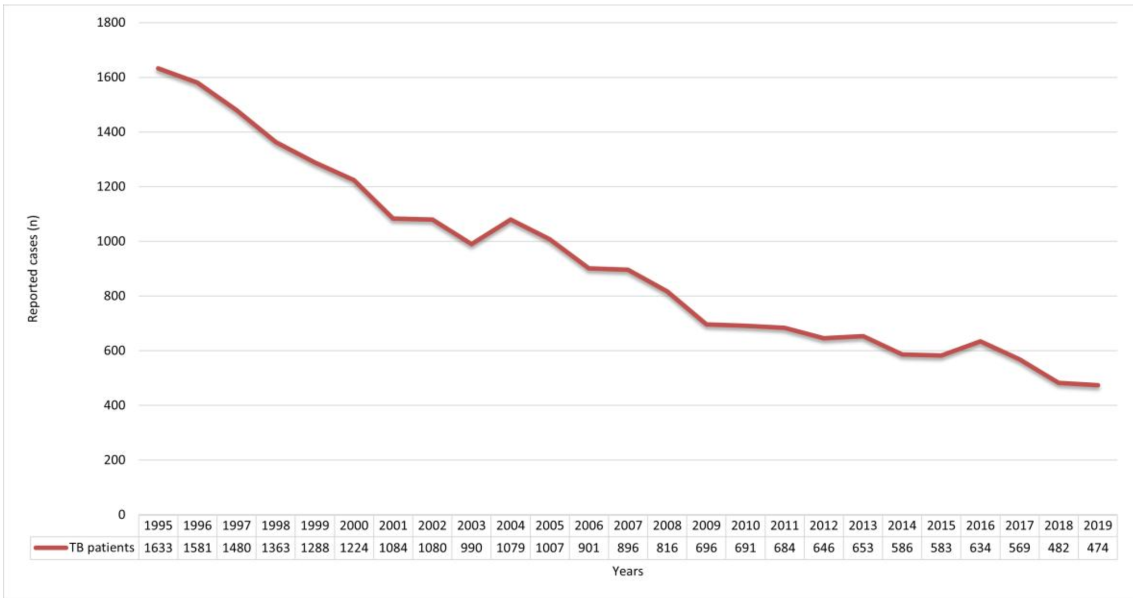


Figure 7. Newly reported TB cases (Austria).

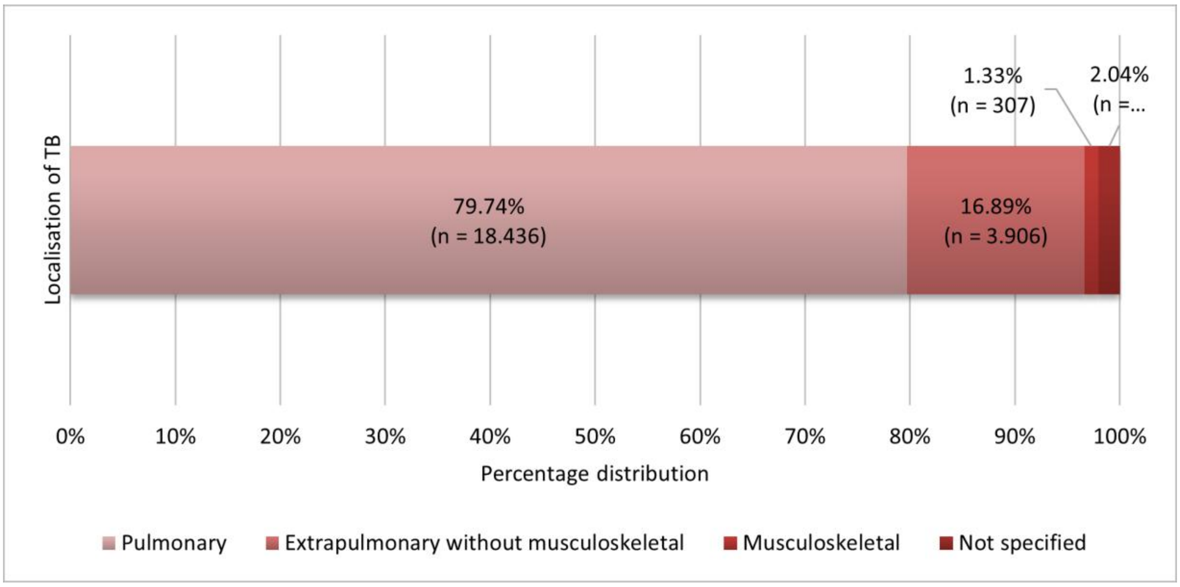


Figure 8. Austrian TB manifestations (1995-2019).

Years	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
TB patients in total	1633	1581	1480	1363	1288	1224	1084	1080	990	1079
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients)										
Pulmonary TB	1230	1264	1161	1072	1016	1008	871	862	826	893
Extrapulmonary TB	249	224	234	243	229	216	203	212	163	181
Not specified	154	93	85	48	43	0	10	6	1	5
Localisation of extrapulmonary cases (n = number of patients)										
Pleura	74	68	68	57	55	50	36	45	27	43
Lymphnodes	84	80	83	95	87	86	95	90	78	85
Urogenital tract	42	36	41	43	32	30	28	31	28	16
Peritoneum, digestive tract	2	5	7	9	11	6	4	7	3	6
Musculoskeletal*	13	11	8	17	15	19	20	17	14	11
CNS + meninges	3	6	4	3	5	3	2	3	2	3
Other organs	24	13	13	14	18	16	12	14	9	17
Disseminated TB	7	5	10	5	6	6	6	5	2	0
** subdivided in:*										
Spinal	*6*	*6*	*3*	*6*	*5*	*13*	*5*	*8*	*5*	*2*
Extraspinal	*7*	*5*	*5*	*11*	*10*	*6*	*15*	*9*	*9*	*9*

Table 2a. Reported TB cases in Austria (1995-2004).

Years	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
TB patients in total	1007	901	896	816	696	691	684	646	653	586
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients)										
Pulmonary TB	810	751	743	679	575	558	534	504	526	479
Extrapulmonary TB	189	144	146	137	121	133	148	142	125	106
Not specified	8	6	7	0	0	0	2	0	2	1
Localisation of extrapulmonary cases (n = number of patients)										
Pleura	37	30	29	23	12	15	20	19	19	22
Lymphnodes	85	72	62	62	61	76	72	72	74	51
Urogenital tract	23	13	21	16	13	5	18	9	6	8
Peritoneum, digestive tract	7	6	3	3	4	10	9	4	9	7
Musculoskeletal*	13	9	12	14	8	10	12	19	6	7
CNS + meninges	2	7	8	4	1	5	3	3	4	4
Other organs	13	7	11	13	18	7	13	16	7	6
Disseminated TB	9	0	0	2	4	5	1	0	0	1
** subdivided in:*										
Spinal	*6*	*4*	*7*	*7*	*4*	*4*	*3*	*10*	*2*	*7*
Extraspinal	*7*	*5*	*5*	*7*	*4*	*6*	*9*	*9*	*4*	*0*

Table 2b. Reported TB cases in Austria (2005-2014).

Years	2015	2016	2017	2018	2019
TB patients in total	583	634	569	482	474
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients)					
Pulmonary TB	457	481	430	364	342
Extrapulmonary TB	126	153	139	118	132
Not specified	0	0	0	0	0
Localisation of extrapulmonary cases (n = number of patients)					
Pleura	25	24	21	15	24
Lymphnodes	65	80	79	68	77
Urogenital tract	4	7	6	8	5
Peritoneum, digestive tract	4	10	4	5	1
Musculoskeletal*	11	17	13	7	4
CNS + meninges	7	5	3	3	5
Other organs	9	9	12	8	9
Disseminated TB	1	1	1	4	7
** subdivided in:*					
Spinal	*6*	*11*	*3*	*3*	*4*
Extraspinal	*5*	*6*	*10*	*4*	*0*

Table 2c. Reported TB cases in Austria (2015-2019).

As shown in tables 2a-2c, organ affections were rather stable over the years recorded. Twenty-five years ago, in 1995, the majority of patients was diagnosed with pulmonary TB (figure 9): In total, 75.32% (n = 1.230) of the reported 1,633 patients were primarily diagnosed with lung involvement. In 236 patients (14.45%), the primary location was an extrapulmonary site. Amongst those, pleural involvement was most common with 4.53% of cases (n = 74), followed by an involvement of extrathoracic lymph nodes in 3.92% (n = 64). In contrast, TB hardly occurred in the digestive tract (including the peritoneum) or the central nervous system (including the meninges) with only two and three reported cases for each of these locations, respectively. The remaining 6.49% of reported cases involved other organ systems such as the urogenital tract (n = 42) or the musculoskeletal system (n = 13; 0.80%). Of note, in 154 patients (9.43%) no organ involvement was specified.

Two years ago, in 2019, a total of 474 new TB cases were recorded in Austria. Again, most of these patients (n = 342; 72.15%) presented with a pulmonary TB manifestation. Extrapulmonary manifestations were seen in 128 patients (27.00%). However, in contrast to 1995, the pleura was not amongst the top three affected organs anymore. Lung affection was followed by involvement of the extrathoracic lymph nodes in 48 cases (10.13%) and an involvement of the intrathoracic lymph nodes in 29 cases (6.15%). Like 1995, the central nervous system including the meninges (n = 5) and the digestive tract (n = 1) were the least frequently involved locations. The remaining 10.34% of TB cases diagnosed in 2019 involved other organ systems, as indicated in table 2a-2c.

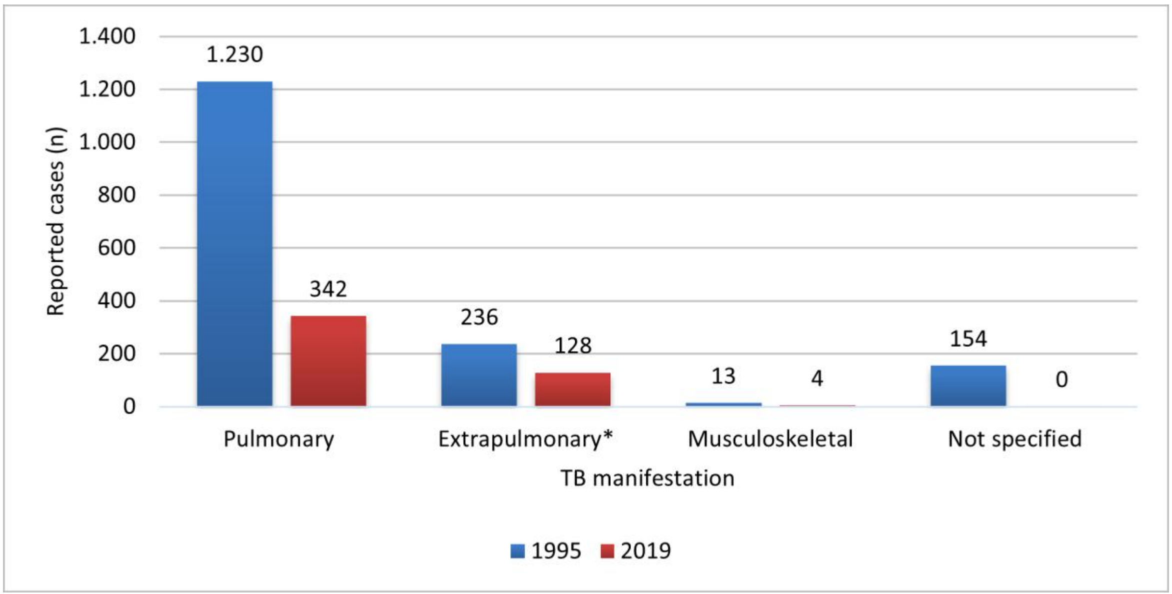


Figure 9. Austrian TB manifestations comparing the years 1995 and 2019.
** Musculoskeletal TB patients are not included.*

3.1.2 Styria

Of the 23,120 tuberculosis patients registered in Austria between 1995 and 2019, 2,874 (12.43%) were recorded in Styria. Again, there was a general downward trend in newly reported cases, which is comparable to the overall Austrian trend, even though some highs and lows were recorded (figure 10): So was the highest number of cases recorded in 1997 with 201 reported cases. A minimum of 51 infected persons was recorded in 2018. Compared to the lowest recorded rate in 2018, 2019 again saw a minor increase in infection rates: so were four more cases recorded in 2019 compared to the previous year, which gives a total number of 55 cases newly diagnosed TB in 2019. However, in 2019, 140 fewer cases were recorded compared to 1995 (71.79%), which confirms a distinct downward trend during our observation period.

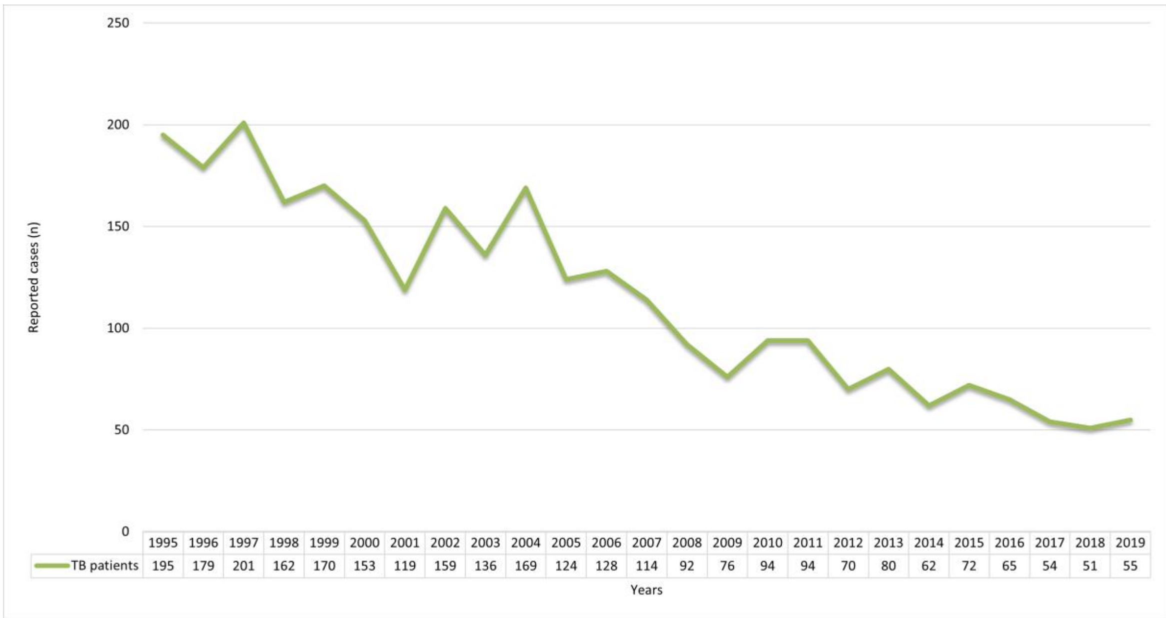


Figure 10. Newly reported TB cases (Styria).

Of these 2,874 newly reported cases in the period observed herein, 79.89% (n = 2.296) were diagnosed with pulmonary TB (figure 11). A total of 442 patients (15.35%) were diagnosed with extrapulmonary involvements. From 1995-2019, 31 cases of musculoskeletal TB were recorded in Styria (1.08%). The distribution of TB sites (pulmonary, extrapulmonary, or musculoskeletal) is shown in more detail in tables 3a-3c.

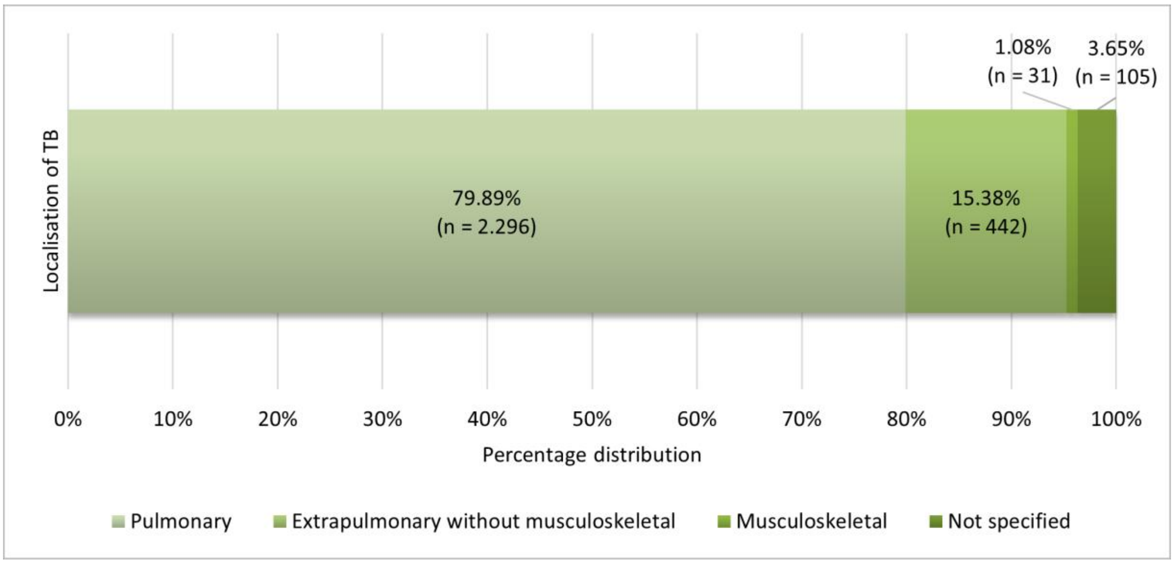


Figure 11. Styrian TB manifestations (1995-2019).

Years	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
TB patients in total	195	179	201	162	170	153	119	159	136	169
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients)										
Pulmonary TB	133	135	151	119	134	130	96	123	111	146
Extrapulmonary TB*	24	23	32	28	28	23	20	36	25	23
Not specified	38	21	18	15	8	0	3	0	0	0
*Musculoskeletal	0	1	2	1	3	3	1	2	1	1

Table 3a. Reported TB cases in Styria (1995-2004).

Years	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
TB patients in total	124	128	114	92	76	94	94	70	80	62
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients)										
Pulmonary TB	100	114	96	76	65	78	78	49	69	57
Extrapulmonary TB*	23	14	18	16	11	16	15	21	11	5
Not specified	1	0	0	0	0	0	1	0	0	0
*Musculoskeletal	0	1	0	2	4	0	0	2	1	1

Table 3b. Reported TB cases in Styria (2005-2014).

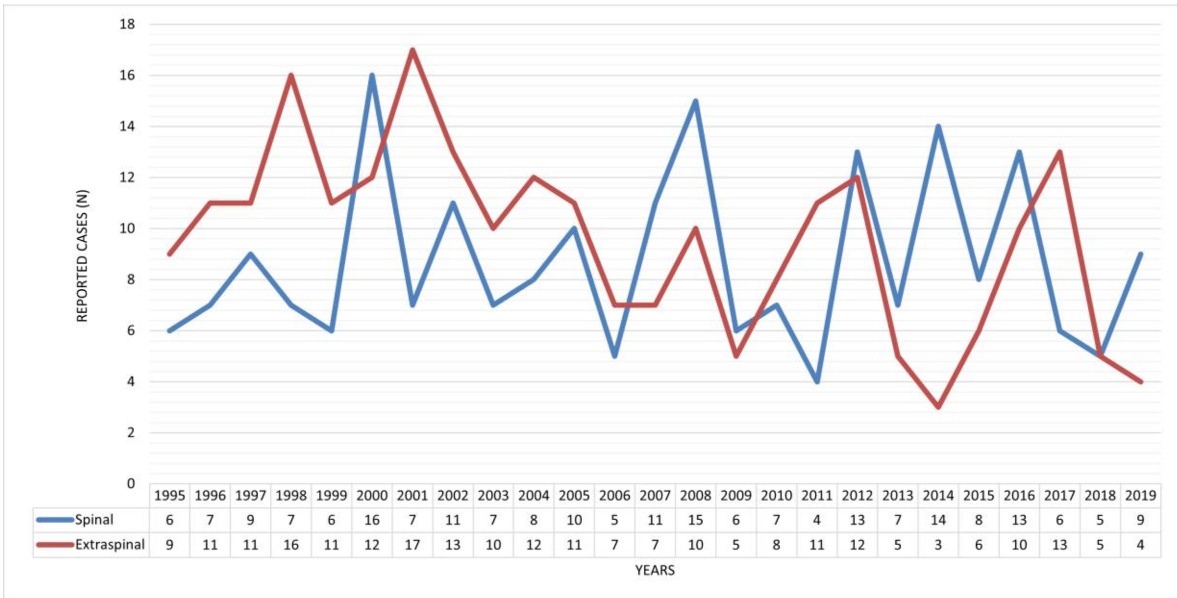
Years	2015	2016	2017	2018	2019
TB patients in total	72	65	54	51	55
Distribution of pulmonary, extrapulmonary vs not specified (n = number of patients					
Pulmonary TB	57	54	39	41	45
Extrapulmonary TB*	15	11	15	10	10
Not specified	0	0	0	0	0
*Musculoskeletal	2	1	2	0	0

Table 3c. Reported TB cases in Styria (2015-2019).

3.1.3 Musculoskeletal tuberculosis

In its data collection, the AGES distinguishes between mainly and additionally affected organs. Furthermore, a distinction is made between spinal and extraspinal musculoskeletal tuberculosis.

Between 1995 to 2019, TB was first diagnosed in the musculoskeletal system in a total of 307 patients in Austria. In these patients, the bone and joints were the sites mainly affected by TB. Amongst those patients, 140 presented with spinal TB ("Pott´s disease"), and 167 presented with extraspinal musculoskeletal TB (figure 12). These patients accounted for 1.33% of the total number of TB cases recorded in Austria in this period. In addition to patients who presented with symptomatic musculoskeletal TB, the bones or joints were co-involved in 149 patients with symptomatic TB of any other site. Amongst those, 77 presented with spinal and 72 with extraspinal manifestations. On average, six new cases of spinal and seven cases of extraspinal bone and joint TB were recorded in Austria between 1995 and 2019 every year.



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Spinal	6	7	9	7	6	16	7	11	7	8	10	5	11	15	6	7	4	13	7	14	8	13	6	5	9
Extraspinal	9	11	11	16	11	12	17	13	10	12	11	7	7	10	5	8	11	12	5	3	6	10	13	5	4

Figure 12. Newly reported cases of musculoskeletal TB in Austria (1995 - 2019).

As shown in tables 3a-3c, 14 spinal and 17 extraspinal cases of bone and joint tuberculosis were diagnosed in Styria since 1995. In all of these patients, the musculoskeletal system was the mainly affected organ. Thus, TB of the musculoskeletal system comprised 1.08% of all TB cases diagnosed in Styria. Spinal or extraspinal involvement was furthermore seen in approximately one patient per year suffering from TB of any other site. In seven out of 25 years, no case of musculoskeletal TB was reported, neither in the category of mainly affected organs, nor in the category of co-affected organs.

3.2 Case series of patients with musculoskeletal TB diagnosed and treated at our institution

As already outlined above (figure 6), a search of our hospital´s electronic registry and a review of the patients´ medical records yielded a total of 17 patients with TB of the musculoskeletal system who were included in our retrospective case series. Subsequently, these patients´ histories will be analysed and followed-up.

3.2.1 Demographical data

3.2.1.1 Gender

This retrospective study includes 17 participants, nine of whom are male (52.94%) and eight of whom are female (47.06%). Thus, musculoskeletal TB shows a slightly male gender preference in our series.

3.2.1.2 Country of origin

More than half of the participants originated from Austria (n = 9; 52.94%). Six participants originated from an Asian country (35.29%). The countries represented were India, Afghanistan, Nepal, Pakistan, and Yemen. Two African countries of origin were also recorded, namely Gambia and Guinea (11.76%) (figure 13).

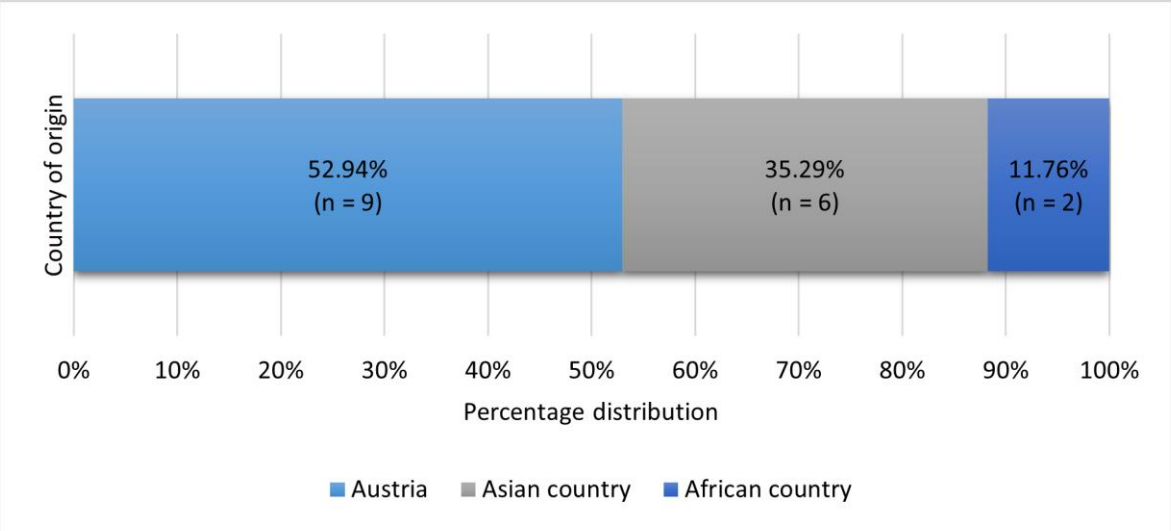


Figure 13. Country of origin of patients with musculoskeletal TB.

3.2.1.1 Age

Age at first diagnosis ranged from 18 to 92 years. We saw two clearly distinguished age groups: patients who were diagnosed under the age of 40 (n = 8; 47.06%) and patients who were diagnosed over the age of 60 (n = 9; 52.94%) (figure 14). On average, patients under 40 were diagnosed at the age of 28 years (with a range from 18-39 years). In contrast, patients over 60 were diagnosed on average at the age of 74 years (with a range from 63-92 years). Particularly younger patients affected by TB had a background of migration (n = 8; 47,06%), whilst all TB patients over 60 were native Austrians (n = 9; 52.94%).

Sex	Age	CO	Location	Lung involvement	Path. Fx	Soft Tissue	Abscess	No. of Bones	Major sympt.	Biopsy	Diagnostic tools	Surgery	Sec. Deform.	FUP months (status)
M	37	G	Spine T	N	N	Y	Y	2	Ne (S)	N	H (-), MB, C	Y	Y	116 (NED)
M	22	Ag	Spine T	N	Y	Y	Y	4	Tu (P)	Y#	H (-), MB, C	N	Y	71 (NED)
M	63	A	Spine Ce, T	Pneumonia, miliary	Y	Y	Y	3	Ne (S)	N	H	N	NA	0 (DOD)
M	29	Ne	Spine L, Sa	Tree-in-bud infiltration	Y	Y	Y	5	S (P)	Y#D	MB, C	N	Y	74 (NED)
M	30	Pa	Spine L	N	Y	Y	Y	1	Ne (P)	Y#	H, MB, C	Y	N	70 (NED)
F	18	Ye	Spine Sa	N	N	Y	Y	4	Tu (Ne)	Y#D	H (-), MB (-), C	N	Y	33 (NED)
F	65	A	Spine T	N	N	Y	N	1	Tu	Y#	H, MB	N	N	29 (NED)
F	69	A	Spine T	Postspecific changes	N	Y	Y	2	Ne (P)	Y#	H, MB, C (-)	Y	Y	105 (NED)
F	69	A	Spine L	Miliary	N	N	N	1	Ne (P)	Y*	H, MB	Y	Y	44 (NED)
F	80	A	Spine L	N	N	Y	N	2	S	N	C	Y	N	5 (DOC)
F	69	A	Tibia	N	N	Y	Y	2	S (P)	N	H	Y	Y	2 (DOC)
F	74	A	MCP1	N	N	Y	N	2	S (P)	N	H, MB, C	Y	Y	47 (NED)
M	39	I	SC joint	Lymphadenopathy	N	Y	Y	2	Tu (S)	Y*	H, MB (-), C	N	Y	61 (NED)
F	81	A	Femur	N	NA	NA	NA	1	S (Fr)	N	H, MB	Y	N	69 (DOC)
M	19	NG	Elbow	Postspecific changes	N	Y	Y	2	S (P)	N	H, MB (-), C	Y	N	15 (NED)
M	29	I	Thoracic wall	Pleuritis	Y	Y	Y	1	Tu (S)	Y**	H, MB, C	Y	N	32 (NED)
M	92	A	Ischium	N	N	Y	Y	1	S (P)	N	MB, C	Y	N	50 (NED)

Table 4. Demographical data, localisation, clinical presentation, surgery, secondary deformities and follow-up in patients presenting with musculoskeletal TB. This table was created by Dr[in] Igrec, Dr[in] Scheipl and Dr[in] Vielgut for the publication resulting from this diploma thesis and is displayed here in a modified version with permission from the authors.

Sex: female (F); male (M). Country of origin (CO): Afghanistan (Ag); Austria (A); Gambia (G); India (I); Nepal (Ne); New Guinea (NG); Pakistan (Pa); Yemen (Ye). Location: thoracic (T); cervical (Ce); lumbar (L); sacral (Sa); first metacarpophalangeal joint (MCP1); sternoclavicular joint (SC joint). Lung involvement: no (N); yes (Y); not applicable (NA). Path. Fx: pathological fracture. Soft Tissue: soft tissue component. Major sympt.: Major symptoms and differential diagnoses: pain (P); neurology (Ne); fracture (Fr); septic process, such as abscess formation or septic arthritis (S); osseous destruction, suspicious of tumourous processes (Tu). Biopsy: open biopsy (*); core needle biopsy (**); CT-guided biopsy (#), with drainage (#D) of an abscess formation. Diagnostic tools: histology (H), molecular biology via PCR (MB), or culture-based verification (C), negative test result (-). Status at last follow-up (FUP): death of other cause (DOC), no evidence of disease (NED), death of disease (DOD).

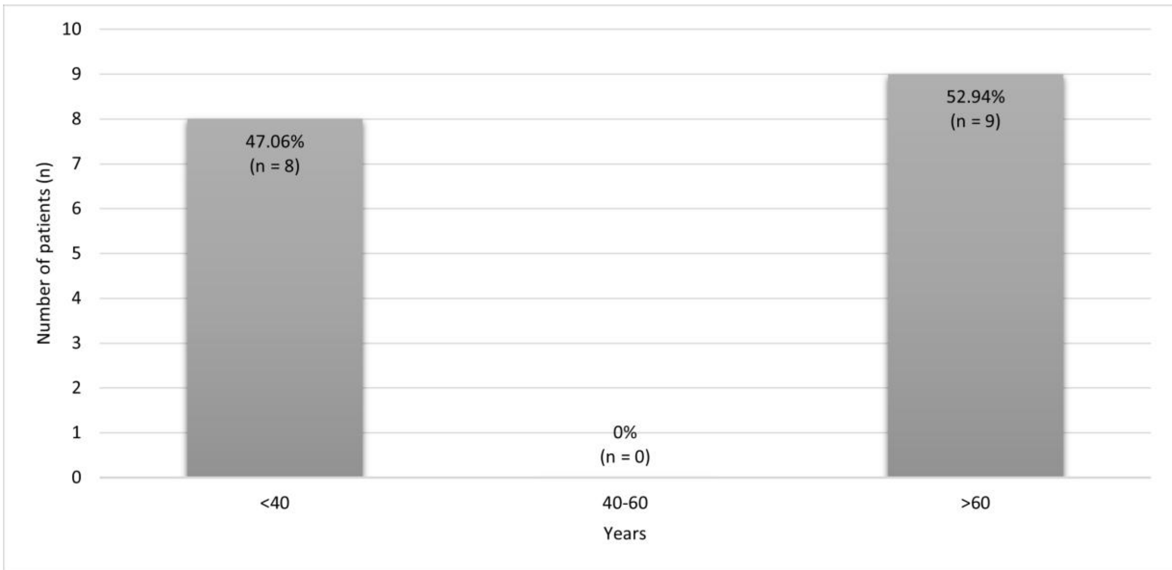


Figure 14. Patients´ age at diagnosis of musculoskeletal TB.

Whereas all patients with a migration background were newly diagnosed with TB during the period investigated herein, two Austrian patients had a previous history of musculoskeletal TB and were diagnosed with a musculoskeletal recurrence. One of these patients had a local recurrence. In the other patient, no exact localisation of the primary disease could be determined retrospectively. Even though none of the 17 patients included in this case series had a known previous history of pulmonary TB, we observed concomitant or post-specific lung affections in seven patients (table 4).

3.2.2 Localisation

In our patient population, ten out of 17 (58.82%) presented with a spinal form of musculoskeletal TB ("Pott´s disease"). The remaining seven (41.18%) had various extraspinal TB localisations (figure 15).

3.2.2.1 Spinal TB localisations

In most patients suffering from spinal TB, the disease occurred in a circumscribed spinal region. However, also multifocal spinal affections were recorded. As shown in table 4, the thoracic and the lumbar spine were most frequently affected. In some cases, an additional involvement of the cervical spine (n = 1) and the sacral region (n = 2) was recorded. Four patients displayed a pathological fracture of an affected vertebra (table 4). In six patients (60%), their spinal manifestation was the sole site of their disease.

Four individuals with spinal affections concomitantly suffered from pulmonary TB (n = 3; 30%) or displayed post-specific pulmonal changes (n = 1; 10%). One of these patients had a severe form of miliary TB additionally affecting several other organs, such as the lung, the spleen, the liver, and the kidneys.

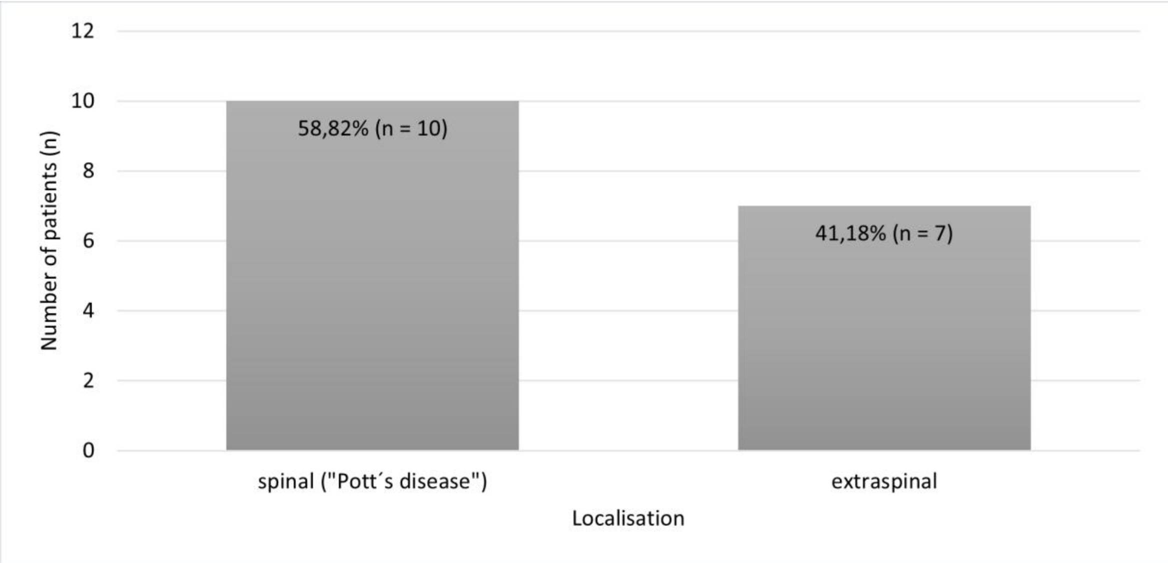


Figure 15. Localisation of musculoskeletal TB (spinal vs extraspinal).

3.2.2.2 Extraspinal TB localisations

In seven patients suffering from extraspinal musculoskeletal TB, sites of clinical manifestation were the bones, joints and soft tissues. So did TB manifest itself in large joints, such as the hip (femur) and the knee joint (tibia), and small joints, including the thumb saddle, the elbow and the sternoclavicular joint, in one case, each. Soft-tissue locations furthermore included the chest wall at its posterior thoracic region between the ninth and the eleventh rib, as well as the gluteal region (ischium) (table 4). Even though TB clinically manifested itself in these joints and soft tissues, a radiographic examination, which was conducted by Dr Jasminka Igrec for a publication resulting from this diploma thesis, displayed a co-affection of the adjacent bones (table 4), so that an osseous origin with secondary joint and soft tissue affection must be assumed. Even though none of these patients showed an active concomitant pulmonary TB, one patient with TB of the elbow joint displayed post-specific pulmonary changes (table 4). Furthermore, the patient presenting with the chest wall involvement showed a concomitant pleuritis, and the patient who suffered from tuberculous arthritis of the sternoclavicular joint also had an involvement of his supraclavicular lymph nodes.

3.2.3 Clinical signs and symptoms

Clinical symptoms at presentation were categorised into three major groups: The most frequently mentioned symptoms at first presentation were septic or inflammatory conditions. Seven patients (41.18%) presented at the outpatient clinic for these reasons. A fair proportion of patients (n = 5; 29.41%) were admitted to our department because of neurological deficits. In the remaining five patients (29.41%), a neoplastic processes was suspected (figure 16, table 4).

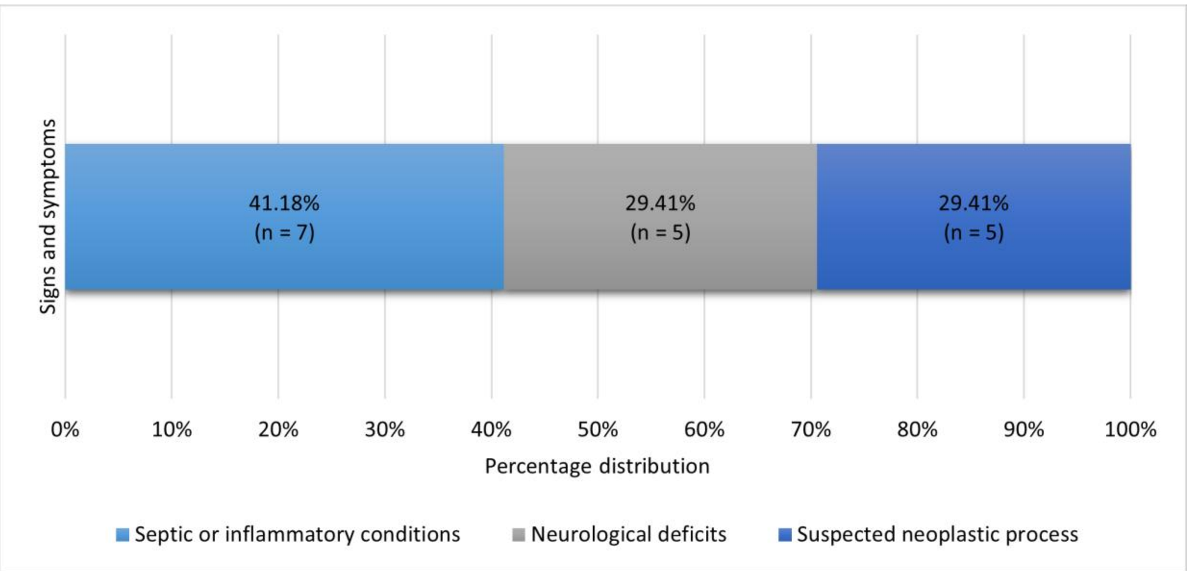


Figure 16. Clinical symptoms of musculoskeletal TB patients.

Regarding the location of their TB infection (spinal vs extraspinal), patients with spinal TB usually presented with neurological deficits and pain (n = 5), inflammatory conditions (n = 2) or suspected neoplastic processes (n = 3), whereas patients with extraspinal TB were admitted due to inflammatory conditions (n = 5) or tumorous soft-tissue swellings of uncertain origin (n = 2) (figure 17).

3.2.1 Time to diagnosis

Most patients of this series (n = 13; 76.47%) were first diagnosed with TB at our institution. TB-specific diagnostic procedures were initiated after a median of 14 days (with a range from 7-405 days) after initial presentation at our department. Four (23.53%) were diagnosed at external hospitals. Two of them already had a confirmed diagnosis of TB when they were admitted to our institution. They had been diagnosed with TB externally seven and 42 days before their initial presentation at our department, respectively. Both patients suffered from extraspinal musculoskeletal TB. They were admitted due to a fistulating abscess formation of the gluteal region and a seroma in the elbow region, respectively.

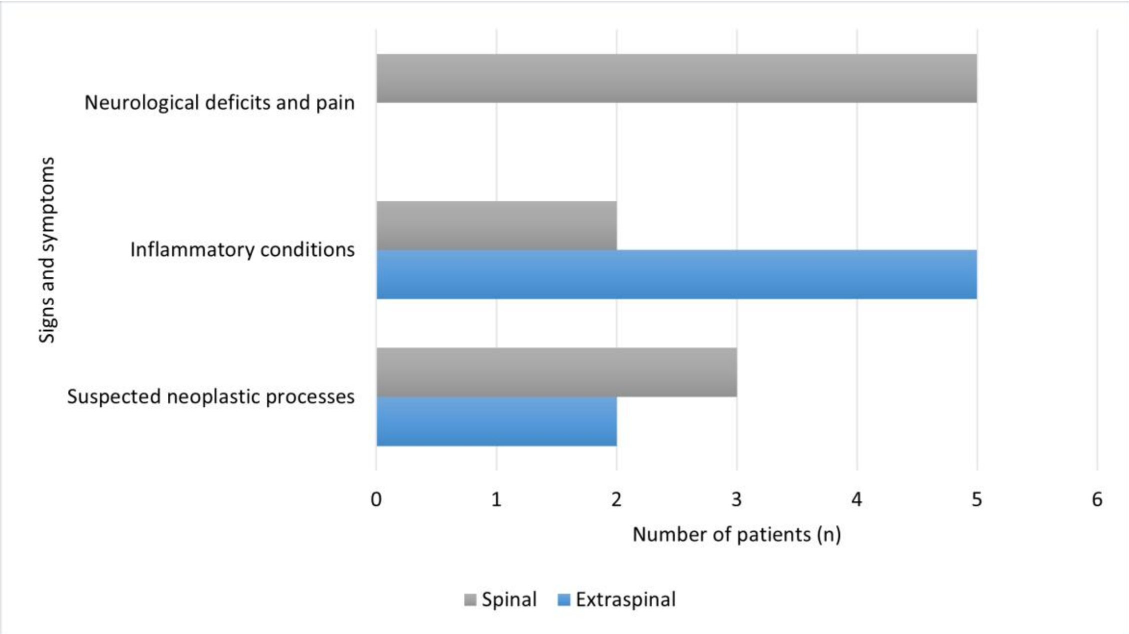


Figure 17. Evaluation of the clinical symptoms according to the location of TB (spinal vs extraspinal).

In the other two patients, TB-specific diagnostic procedures were initiated in external hospitals five and 114 days after their initial presentation at our department. In one of these patients, miliary TB was confirmed in an external post-mortem examination, which was conducted five days after the patient had been admitted to our department for a consultant opinion. In the other patient, however, diagnosis was delayed because an MRI was ordered at initial presentation and the patient did not return for a discussion of the findings until three and a half months later.

As illustrated in figure 18, spinal TB, was diagnosed after a median of 31 days (with a range from 7-405 days). Even though neurological deficits resulted in an earlier diagnosis in some of these patients, others presented with unspecific symptoms (see chapter 3.2.3 "Clinical signs and symptoms") which often resulted in an extended time to diagnosis. In comparison, extraspinal musculoskeletal TB, which frequently presented as a suspected joint infection or neoplastic process, was diagnosed after a median of 22 days after initial presentation (with a range from 10-74 days), i.e. nine days earlier (figure 18).

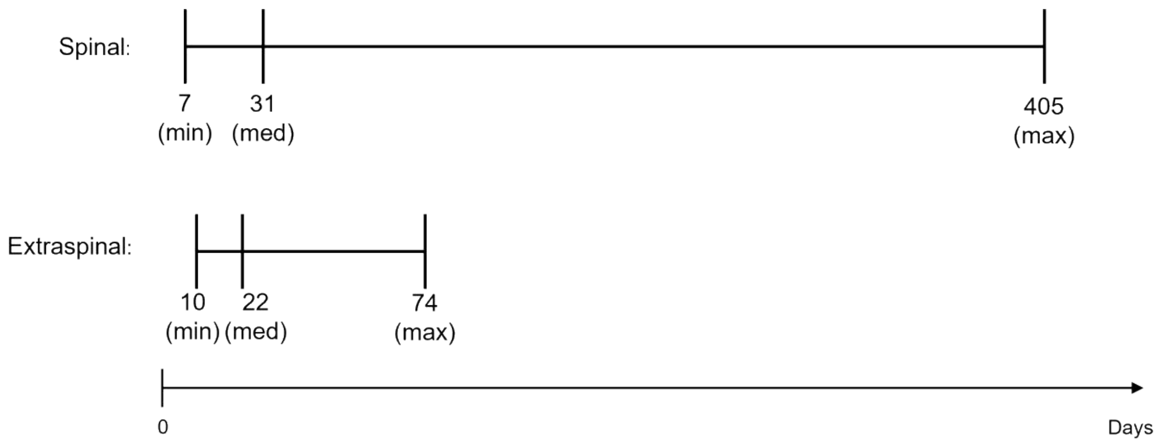


Figure 18. Schematic representation of the period from initial presentation (spinal vs extraspinal musculoskeletal TB) at our department to diagnosis (via histology, molecular biology, or culture). Abbreviations: minimum (min), median (med) and maximum (max).

3.2.2 Diagnosis

As outlined above (see chapter 1.8 “Diagnostic tools”, page 8), the following diagnostic tools were applied for confirmation of TB: microscopic examination of infected tissue, culture-based verification of the tubercle bacillus, or molecular tests for detection of mycobacterial DNA (PCR).

All three diagnostic methods were used in nine out of 17 patients (52.94%) (table 4). Of these nine patients, all results were positive in three patients. In five out of nine patients, one of three tests was negative: either the histology (n = 2), the PCR test (n = 2), or the culture-based verification (n = 1). In one of these nine patients, both histology and PCR were negative, but TB was culture-verified. In five out of 17 cases (29.41%), only two diagnostic tools were applied, either histology and PCR (n = 3), or PCR and culture (n = 2), all of which were positive. In the remaining three cases, only one confirmed diagnostic method was used. Twice the diagnosis was confirmed with positive histology and once with a positive culture.

As shown in table 4, the diagnostic material was obtained via biopsy in nine cases (52.94%). Seven of these patients showed spinal involvement and were diagnosed via CT-guided punctures (n = 6) and open biopsy (n = 1). As part of CT-guided biopsy, received two patients drainage of their abscess formations. An open biopsy and a core needle biopsy were taken in one patient each, with extraspinal manifestations (table 4). In five patients, the biopsy was conducted to rule out neoplastic lesions. Because of neurological deficits and septic processes were three and one patient punctured, respectively. In seven patients (41.17%) who did not undergo biopsy, sampling of diagnostic material was conducted during surgery. Six of them were operated on due to septic processes such as abscess formation or septic arthritis and one patient was operated on due to his severe neurological symptomatic. One patient died of multiorgan failure due to miliary TB. In this case, musculoskeletal TB was clinically suspected and (histologically) confirmed by an autopsy.

3.2.3 Treatment

In our case series, we distinguished between a purely conservative treatment (i.e., drug therapy alone) and the combination of drug treatment with a surgical intervention. Six patients received a purely conservative treatment (35.29%), whereas the remaining eleven patients (64.71%) additionally underwent surgery (figure 19).

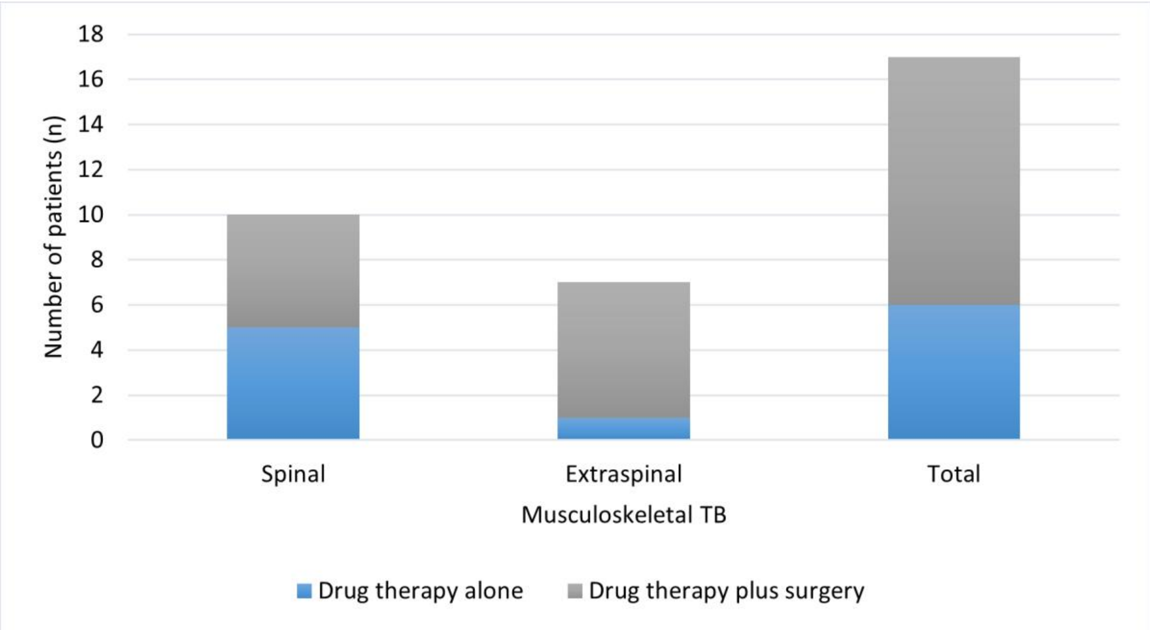


Figure 19. Type of treatment: drug therapy alone vs drug therapy plus surgery.

3.2.3.1 Drug treatment

The standard treatment regimen consisted of a combination of four drugs, namely isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB). According to this regimen, INH, RMP, PZA und EMB should be administered for two months, and a combination of INH and RMP for another seven months after the initial quadruple drug regimen. (18) During drug treatment, patients were monitored via regular clinical examinations and blood tests (checking inflammation parameters, liver enzymes and kidney function). Furthermore, a specialist ophthalmological check-up was conducted during the intake of EMB.

As shown in table 5, eleven patients (64.71%), six with spinal involvement and five with extraspinal involvement, received this standard drug treatment regimen. Two patients (11.76%) with spinal involvement were treated with a different four-drug regimen. One received streptomycin instead of INH due to massive seizures presumably caused by INH, the other one was given moxifloxacin instead of RMP due to a fulminant increase in liver transaminases. Side effects (hepatopathy and itching, respectively) were also the reason why two patients with extraspinal TB (11.76%) received a triple-drug therapy with RMP and INH plus EMB. In one patient (5.88%) with spinal TB, EMB was omitted without a known reason. One patient (5.88%) did not receive any drug therapy due to severe pre-existing adverse health conditions. The same patient died of cardio-respiratory insufficiency within a few days after the initial presentation at our department.

Drug treatment	**Spinal (n)**	**Extraspinal (n)**	**Total (n)**
Standard medication (quadruple)	6	5	11
Other quadruple medication combination	2	0	2
Standard medication (triple)	1	2	3
No drug therapy	1	0	1

Table 5. Drug treatment of patients with musculoskeletal TB.

3.2.3.2 Surgical treatment

In total, eleven patients (64.71%) underwent a surgical intervention due to their musculoskeletal TB manifestation (table 4). Five of these patients had a spinal TB manifestation (45.45%). The main reasons for surgery in this group were neurological deficits (n = 4) and advanced local osseous destructions (n =1). Four patients underwent a (hemi-)laminectomy and stabilization. The fifth patient developed a progressive kyphotic spinal deformity with incipient paraplegia during conservative TB treatment. He was treated with a corpectomy and implantation of an obelisk cage.

Six patients with extraspinal TB were treated for joint infections, necrosis of the affected area, or extensive abscess formations (table 4). These patients underwent joint lavage, synovectomy, necrectomy, and debridement of periarticular abscess formations. One patient had a removal of her trapezium due to a severe osseous destruction caused by TB. Another patient received a hip replacement due to a non-recent fracture of the femoral neck caused by chronic, TB-induced osteomyelitis and necrosis.

Six patients with spinal and three with extraspinal TB manifestations (in total: n = 9; 52.94%) developed a secondary deformity regardless of whether they had surgery or not (table 4).

3.2.4 Follow up

At last follow-up in December 2020, 13 patients showed no evidence of disease (76.47%) (table 4). Three patients had died of other causes (17.65%). One patient with miliary TB died of disease (5.88%). No patient was lost of follow-up (table 4).

3.3 TB prevention for clinical staff

Prevention strategies differ between pulmonary and extrapulmonary TB, as the risk of infection is significantly increased in pulmonary TB due to its potential aerogenic spread. Patients with infectious pulmonary TB must be placed in isolation with room air cleaning until the sputum is confirmed to be TB negative (three subsequent microscopically confirmed negative tests). In contrast, isolation is not required in patients with extrapulmonary TB. (21)

Furthermore, patients with pulmonary TB should wear facial masks covering their nose and mouth during contacts with other people. Also clinical staff and visitors should use a filtering face piece of at least the second protection class (FFP2 mask) during contacts with these patients. In extrapulmonary TB without lung involvement, FFP2 masks are usually not necessary. (21)

Protective gowns (only for pulmonary TB) and protective gloves must be worn during patient contact or contact with body excretions, blood, or other infectious materials (e.g. wound secret, pus). For disinfection of potentially contaminated surfaces tuberculocidal agents should be used; these need to be removed with the infectious waste. (21)

Chemoprophylaxis is only required for vulnerable people after unprotected direct contact with infectious patients with pulmonary TB due to the risk of aerogenic transmission. However, chemoprophylaxis is not necessary for extrapulmonary TB as there is a low infection risk. (21)

3.4 TB reporting process

Since March 1968, Austria has a federal law to combat tuberculosis, the so-called "Tuberculosis Act" (Federal Law Gazette No. 127/1968, available at https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10010326; last accessed 02/20, 2022). This law regulates the obligation to report TB and the procedure of reporting. Paragraphs three to five state that doctors are obliged to report every novel case of TB, every case of suspected TB in a patient who refuses further diagnosis or treatment, and any case of death caused by TB to the competent authorities. Reports can be submitted in written form or electronically. If the patient is a permanent resident of Austria, reports should be submitted to the district administrative authorities of the patient´s place of residence. If the patient does not permanently reside in Austria, the authorities of the patient´s current Austrian area of residence need to be informed. (22)

To fulfil this statutory obligation, the notification form (available at https://www.ris.bka.gv.at/Dokumente/Bundesnormen/NOR40192287/II_101_2017_Anlage.pdf; last accessed 02/20, 2022) (also see supplement 4) must be filled in by the attending physician and sent to the competent authorities.

4 Discussion

4.1 Austrian TB registry data analysis (1995-2019)

According to the data provided by the Austrian Agency for Health and Food Safety, we saw an almost linear decline in the number of newly reported cases in Austria since 1995. Whereas 1.633 cases were reported in 1995, only 474 cases were reported in 2019. This results in an incidence rate of 20.55 per 100.000 people in 1995, compared to 5.34 per 100.000 people in 2019.

Although there is an overall decrease in TB numbers in Austria, an increase of the extrapulmonary proportion has been reported across Europe. (23) So did Sandgren et al 2013 analyse pooled European registry data and observed rising proportion of extrapulmonary TB across Europe, which include musculoskeletal manifestations. While extrapulmonary TB numbers are rather stable over the years from 2002 to 2011, a decrease of pulmonary TB cases has been reported. This led to a percentage increase in extrapulmonary TB numbers. (23) Hayward et al 2021 suggests that this increase in extrapulmonary TB is related to migration, as migrants have a higher proportion of extrapulmonary cases.(24)

In the Austrian province of Styria, which was examined more closely in this work, a similar picture emerges regarding cases of newly reported TB: Compared to 1995 with 195 reported cases, only 55 cases were recorded in 2019, i.e., 71.79% fewer than in 1995. Like the rest of Austria, Styria saw a continuous decline in TB numbers throughout our observation period.

Between 1995 to 2019, TB was first diagnosed in the musculoskeletal system in a total of 307 patients (1.33%) across Austria. Thus, musculoskeletal TB was the fourth most common extrapulmonary TB manifestation in this country (7.29% of all extrapulmonary cases). Other authors report similar percentages for other countries, for instance, Jutte et al 2004 for The Netherlands with 10.6% or Peto et al 2009 for the United States of America with 11.3%. (25,26) Amongst musculoskeletal cases of TB, spinal manifestations were more common than extraspinal TB. (27,28)

4.2 Retrospective analysis of TB patients treated at the Department of Orthopaedics and Trauma, Medical University of Graz, between 2005 and 2019

Our study group consisted of 17 patients with confirmed musculoskeletal TB, which were identified retrospectively based on a search of the hospital´s electronic database. This group consisted of nine men (52.94%) and eight women (47.06%). Even though our group was small, these data are in line with other literature reports which see a slight male predominance amongst patients with musculoskeletal TB. (29) Furthermore, we observed two distinct age groups: The first group consisted of eight patients who were aged under 40 years (with a range from 18-39 years). All of these younger patients had a migration background. The second group consisted of elderly people, as all participants (n = 9) were aged over 60 years (with a range from 63-92 years). All of them were native Austrians (table 4). A similar age distribution with biphasic peak is shown by other authors, e.g., by Hayward et al 2021, who also observed that migrants were younger at diagnosis of extrapulmonary TB compared to non-migrants. (24)

Ten out of our 17 participants (58.82%) presented with a spinal form of musculoskeletal TB ("Pott´s disease"), whereas the remaining seven patients (41.18%) had various extraspinal TB localisations. Similar distributions are also found in the literature, as a predominance of spinal musculoskeletal TB was reported for instance in France (59.5%), Denmark (54.3%), and The Netherlands (56%). (25,27,28) In line with the literature, most spinal cases were reported in the thoracic spine, followed by the lumbar and the cervical spine. (28,30) Sites of clinical manifestation of extraspinal TB were the joints and soft tissues. However, an analysis by our radiologist, Dr Jasminka Igrec, displayed an osseous origin from the adjacent bones with secondary joint and soft tissue affections (table 4), which is supported by the published literature. (31-33) For instance, Jeyaseelan et al 2015 describe a case of midfoot affection caused by osseous TB of the cuboid bone (32), and Papagelopoulos et al 2005 outline a patient with tuberculous sacroiliitis who presented with a gluteal abscess formation. (33)

A multicentric study in France compared, the duration of diagnosis in patients with spinal and extraspinal TB. According to this study, patients with spinal TB were diagnosed after a median of four months, whereas patients with extraspinal TB were diagnosed two months later. (27) In contrast to this study by Guillouzouic et al 2020, diagnostic confirmation of spinal TB took longer than diagnosis for extraspinal TB in our cohort. (27) Spinal TB was diagnosed after a median of 31 days (with a range from 7-405 days) in our patients. In comparison, extraspinal musculoskeletal TB was diagnosed at a median of 22 days after initial presentation (with a range from 10-74 days), i.e., nine days earlier. We think that this might be because extraspinal musculoskeletal TB frequently presented as a suspected joint infection or neoplastic process in our patients, so that additional diagnostic steps were immediately taken. In contrast, patients with spinal TB often presented with unspecific symptoms and pain which often resulted in a diagnostic delay, even though neurological deficits resulted in an earlier diagnosis in some patients. In general, delays in the time to diagnosis are often reported in TB, as the symptoms, particularly of musculoskeletal TB, are rather unspecific. (12,34)

In line with AWMF and WHO recommendations (18,35), the vast majority of our patients (16 out of 17; 94.12%) received an antituberculosis drug therapy. Only one patient did not receive any drug therapy due to severe pre-existing adverse health conditions. He died shortly after initial presentation to our hospital. According to the official recommendations, antituberculosis drug therapy consisted of INH, RMP, PZA, and EMB, which should be administered for two months, followed by a combination of INH and RMP for another seven months. (18) In about one third of our patients (n = 5), variations of this treatment regimen were required due to side effects of the medication. In two cases, one drug was replaced by another equivalent drug and in the remaining three cases, the drug causing the side effect was omitted.

However, drug therapy prevents surgical intervention only if therapy is initiated in a very early stage. (14) Unfortunately, diagnosis of musculoskeletal TB is delayed by several months in many patients as a result of unspecific symptoms. Neither do patients attend a doctor, nor do physicians consider TB as a potential differential diagnosis at early stages of the disease due to its unspecific signs. (27,34) As outlined above, our data confirms these delays in diagnosis, as most patients were admitted to our department in an advanced symptomatic stage of their disease.

Subsequently, eleven (64.71%) of our patients underwent a surgical intervention. The main causes for surgery were septic conditions (n = 7; 63.64%) and neurological deficits (n = 4; 36.36%). Four patients with spinal TB underwent a (hemi-)laminectomy and stabilization. During drug therapy another patient with spinal TB developed a progressive kyphotic deformity with incipient paraplegia, which was treated with a corpectomy and implantation of an obelisk cage. This is in line with literature recommendations stating that surgery in spinal TB can be restricted to patients with neurological deficits or progressive deformities. (36) Six patients with extraspinal TB were treated for joint infections, necrosis of the affected areas, or extensive abscess formations. These patients underwent joint lavage, synovectomy, necrectomy, and debridement of periarticular abscess formations. Again, these data are consistent with the literature, as many reported cases of advanced extraspinal musculoskeletal TB presented as joint infections of bone necroses requiring surgical interventions. (37,38)

By the end of our observation period in December 2020, 13 patients showed no evidence of disease (76.47%). Retrospectively, three patients had died of other causes (17.65%) and only one patient died of miliary TB (5.88%) (table 4). These findings are supported by the literature, as patients with musculoskeletal TB can usually be cured by proper, consequent drug treatment and seldom succumb to their disease. (31)

4.3 TB prevention and reporting

Overall, the risk of infection is comparatively low in extrapulmonary TB, as the spread of TB bacilli is predominantly caused by aerogenous transmission in pulmonary involvement. (21) Once a pulmonary involvement has been ruled out in TB patients, no chemoprophylaxis is necessary for vulnerable healthcare workers. (21) However, if immunocompromised healthcare workers have been in unprotected contact with a patient suffering from active TB with pulmonary involvement, chemoprophylaxis is required. This chemoprophylaxis should be started immediately and consists of INH 300 mg daily for eight weeks. After this period, a tuberculin skin test or IGRA is necessary to decide whether further antituberculosis treatment is necessary or not. (18)

Furthermore, physicians are obliged by law to report any case of newly diagnosed TB, suspected TB in patients who refuse further diagnosis or treatment, or death of TB. (22) For this purpose, the TB notification form in supplement S4 must be completed by the attending physician and sent to the competent authorities.

4.4 Limiting factors

Our study was conducted with patients from a single hospital. Nevertheless, this hospital is the largest in the region and is specialised in infectious diseases and musculoskeletal tumours. Based on this, it can be assumed that most patients with musculoskeletal TB in the southeast of Austria were treated with our support. Furthermore, the rest of Austria represented at least in data from the national Austrian registry.

Due to the retrospective study design, we could not determine exactly how long these patients had been symptomatic before their initial presentation at our department. However, as we closely collaborated with private practitioners, lung specialists and specialists for infectious diseases, we were able to obtain precise information about the treatment course and follow-up of our patients.

5 Conclusion

This study illustrates once more that TB is far from being eradicated in Austria. To avoid delays in treatment and secondary complications, it is essential to diagnose the disease as early as possible. Therefore, TB must remain in the minds of the treating physicians as a differential diagnosis, especially in cases of atypical joint infections or unspecific bone lesions.

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7 Supplement

Table S1: Newly reported cases of TB in Austria from 1995-2019 divided into mainly affected (A) and additionally affected organs (B) with kind permission of the Austrian Agency for Health and Food Safety, 11/11/2020

Table S2: Newly reported cases of TB in Styria from 1995-2019 divided into mainly affected (A) and additionally affected organs (B) with kind permission of the Austrian Agency for Health and Food Safety, 11/11/2020

Table S3: Austrian TB incidence rates from 1995-2019

Form S4: Notification form for reporting a new case of TB in Austria

Supplement 4:

MELDUNG gemäß § 3, 4, 5 und 11 des Bundesgesetzes vom 14. März 1968 zur Bekämpfung der Tuberkulose (TUBERKULOSEGESETZ), BGBl. Nr. 127/1968 idgF

Absender/in:

…………………………………………………………….

…………………………………………………………….

…………………………………………………………….

An die/den

Bezirkshauptmannschaft/Magistrat – Gesundheitsamt

…………………………………………………………….

Porto zahlt Empfänger!

MELDUNG über

eine ansteckende Tuberkulose[1]	☐
eine nicht ansteckende Tuberkulose[2]	☐
einen Krankheitsverdacht[2], wenn sich die krankheitsverdächtige Person der endgültigen diagnostischen Abklärung entzieht	☐
einen Todesfall, wenn anlässlich der Totenbeschau oder Obduktion festgestellt wurde, dass im Zeitpunkt des Todes eine ansteckende Tuberkulose bestanden hatte[4]	☐
War die Tuberkulose Todesursache? ☐Ja ☐ Nein	
einen positiven Nachweis eines Tuberkuloseerregers (Mehrfachnennungen möglich)	☐
a) mikroskopischer Nachweis von säurefesten Stäbchenbakterien in einer klinischen Probe ___________________________(Angabe des Probenmaterials)	☐
b) Nukleinsäure Nachweis von tuberkulösen Mykobakterien in einer klinischen Probe ___________________________(Angabe des Probenmaterials)	☐
c) Kultureller Nachweis von tuberkulösen Mykobakterien in einer klinischen Probe ___________________________(Angabe des Probenmaterials)	☐
d) Nachweismethode nicht bekannt _______________________________(Name des Nachweisführenden)	☐
IGRA („Interferon-Gamma-Release-Assay“) ☐positiv ☐ negativ ☐ nicht durchgeführt	
Tuberkulin Hauttest ☐positiv ☐ negativ ☐ nicht durchgeführt	
Pulmonale Tuberkulose	☐

[1] Eine ansteckende Tuberkulose liegt vor, wenn eine Infektion mit einem Tuberkuloseerreger beim Menschen und eine aktive Erkrankung vorliegen und Tuberkuloseerreger ausgeschieden werden (bestätigter Tuberkulosefall). 2 Eine nicht ansteckende Tuberkulose liegt vor, wenn eine Infektion mit einem Tuberkuloseerreger beim Menschen und eine aktive Erkrankung vorliegen, aber keine Tuberkuloseerreger ausgeschieden werden.

[2] Ein Krankheitsverdacht liegt vor, wenn bis zur endgültigen diagnostischen Abklärung nach dem Stand der medizinischen Wissenschaft begründete Anhaltspunkte für das Vorliegen einer Tuberkuloseerkrankung gegeben sind.

4 Todesfälle sind auch dann zu melden, wenn der Todesfallmeldung bereits eine Erkrankungsmeldung vorangegangen ist.

Extrapulmonale Tuberkulose	☐
Betroffenes Hauptorgan Zusätzlich betroffene/s Organ/e Begleiterkrankungen	……………………………… ……………………………. ………………………………
Therapie (Antituberkulotika)	………………………………
Datum der Diagnose	__:__:___
Datum des Todes	__:__:___
Familienname Vorname Geschlecht Geburtsdatum Geburtsort Staatsangehörigkeit Datum der Einreise nach Österreich (falls zutreffend) Wohn- oder Aufenthaltsadresse Telefonnummer SVNR SV-Träger Arbeitsstätte / Schule / Gemeinschaftseinrichtung	………………………………………………………………………. ………………………………………………………………………. □ Männlich □ Weiblich ……………………………. ……………………………… ……………………………… ……………………………… ……………………………… ……………………………. ……………………………… ……………………………… ……………………………. ……………………………… ……………………………… ………………………………………………………………………. ………………………………………………………………………. ……………………………………………………………………….
Krankenhausaufenthalt Wenn ja, Datum der Aufnahme und Bezeichnung der Krankenanstalt	Ja □ Nein □ ………………………. ……………………….
Weitere Anmerkungen (sofern erforderlich und verhältnismäßig) …………………………………………………………………………….	

………………………………………., den ……………………………….
Ort und Datum

…………………………………………………………………………
Unterschrift, Adresse und Telefonnummer der/des Anzeigenden