Health-Related Quality of Life (HRQOL) of Multidrug-Resistant Tuberculosis (MDR-TB) Patients and its applicability to MDR-TB patients Living in Yangon Region, Myanmar

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TITLE

A thesis submitted in partial fulfilment of the requirement for the degree of

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by

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Abbreviations

ADR	Adverse Drug Reactions
Bdq	Bedaquiline
BMC	Baseboard Management Controller
BP	Bodily Pain
CBTBC	Community-Based Tuberculosis Care
CI	Confidence Interval
CMD	Common Mental Disorder
DALYs	Disability-Adjusted Life Years
Dlm	Delamanid
DM	Diabetes Mellitus
DOTS	Direct Observed Treatment, Short Course
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
DSTB	Drug Susceptible Tuberculosis
EPTB	Extra-pulmonary Tuberculosis
FGDs	Focus Group Discussions
GDP	Gross Domestic Product
GH	General Health
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HRQOL	Health-related Quality of Life
IEC	Information, Education, Communication
LTBI	Latent Tuberculosis Infection
MCS	Mental Component Summary
MDR-TB	Multidrug Resistant Tuberculosis
M	Mean
MH	Mental Health
MoHS	Ministry of Health and Sport
NBS	Normal Based Scoring
NCBI	United State National Library of Medicine
NCDs	Non-communicable diseases
NHP	National Health Plan
NRITLD	National Research Institute of Tuberculosis and Lung Disease
NSP	National Strategic Plan
NTP	National Tuberculosis Control Program
OR	Odds Ratio
PCS	Physical Component Summary
PF	Physical Functioning
PLHIV	People Living with Human Immunodeficiency Virus
PLOS	Public Library of Science
PMC	PubMed Central Databases
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
PTB	Pulmonary Tuberculosis
QOC	Quality of Care
QOL	Quality of Life
RE	Role Emotional
RF	Role Functioning
RL	Role Limitation
RP	Role Physical

RR-TB	Rifampicin Resistant Tuberculosis
Rs.	Rupees (Indian Currency)
SD	Standard Deviation
SDGs	Sustainable Development Goals
SEAR	South-East Asia Region
SES	Socio-Economic Status
SF	Social Functioning
SF-8	Short Form Survey-8
SF-12	Short Form Survey-12
SF-36	Short Form Survey-36
SSIs	Semi-Structured Interviews
STR	Shorter Treatment Regimen
TB	Tuberculosis
TSR	Treatment Success Rate
UHC	Universal Health Coverage
VT	Vitality
VU	Vrije Universiteit Amsterdam
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life-BREF
WHOQOL-HIV	World Health Organization Quality of Life-Human Immunodeficiency Virus
WPR	Western Pacific Region
WRD	World Health Organization Approved Rapid Molecular Diagnostic Test
XDR-TB	Extensive Drug-resistant Tuberculosis

Definition of terms used

1. Pulmonary tuberculosis (PTB)[1]
   "Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree".

2. Extrapulmonary tuberculosis (EPTB)[1]
   "Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges".

3. New patients: "have never been treated for TB or have taken anti-TB drugs for less than 1 month"[1].

4. Previously treated patients: "have received 1 month or more of anti-TB drugs in the past"[1].

5. Relapse patients: "have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)"[1].

6. Patients with unknown previous TB treatment history: "do not fit into any of the categories listed above"[1].

7. HIV-positive TB patient
   "Refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started"[1].

8. HIV-negative TB patient
   "Refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis"[1].

9. HIV status unknown TB patient
   "Refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care"[1].

10. Treatment success rate (TSR)[1]
    The sum of cured and treatment completed.

    "Cured: treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase".
    "Treatment completed: treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase".

11. Patient-centred approach[2]
    "Treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider".

12. Community–based TB care (CBTBC)[2]
    "Activities cover a wide range of activities contributing to prevention, diagnosis, improved treatment adherence and care that positively influence the outcomes of drug-susceptible, drug-resistant and HIV-associated TB. The activities also include community mobilization to promote effective communication and participation among community members to generate demand for TB prevention, diagnosis, treatment and care services".

13. Community health workers or community volunteers[2]
    "They carry out community-based TB activities, depending on national and local contexts. They are people with some formal education who are given training to contribute to community-based health services, including TB prevention as well as patient care and support and their time is often compensated by incentives in kind or in cash".

14. Social support[2]
    "Refers to the person's perception and confirmation that he/she is part of a social network that cares for him/her. Social support is determined by access to four resources: Informational support, emotional support, Companionship support and material support".

15. Universal Health Coverage (UHC)[3]
    "UHC is defined as all people having access to needed health services of quality without experiencing financial hardship".

Glossary

1. Stigma: "the perception of guilty or sufferings or experiences due to MDR-TB that directly comes from the stigmatized patient with MDR-TB"[4]

2. Adverse Drug Reactions (ADRs): "is a response to a TB medicine which is noxious and unintended, and which occurs at doses normally used in humans"[2].

Abstract

Introduction: Multi-drug resistant tuberculosis (MDR-TB) is a global public health concern, and Myanmar also has important long-term MDR-TB problems. It is still featuring on "30 high MDR-TB burden" countries list with a higher occurrence rate (5.1% in new TB and 27% in previously treated TB cases) than the global average. Tuberculosis (TB) and MDR-TB are listed as a country prioritized disease but currently, the majorities of research studies are mainly focusing on clinical aspects, so the disease impacts on the quality of life (QOL) of patients in a still neglected area and it needs to be explored.

Objectives: To explore the most likely factors influencing and impacting on QOL of MDR-TB patients, to make recommendations to the National Tuberculosis Control Program (NTP) and the Ministry of Health and Sports (MoHS) that can be piloted to improve and address the problems in Myanmar.

Methodology: A comprehensive literature review by search strategy and snowball approach to look for literature published between 1990 and 2019.

Findings: The main findings were TB and MDR-TB that had long-term negative impacts on QOL, which put some weights on physical problems, psychological distress and socio-economic burden, imposed by disease-related symptoms, treatment-related side-effects, social stigma and discrimination resulting into a vicious poverty cycle and a low QOL.

Conclusions: An integrated health care approach, with community participation, are needed in providing quality of care (QOC) and a package of support (diagnosis and treatment, counselling, health education, nutritional, psychosocial and financial support) which will substantial improve the patients' QOL.

Keywords: TB, MDR-TB, QOL, Health-related quality of life (HRQOL)
Word count – 12,218

Introduction

My name is Sandi Tun, I am a medical doctor, who is a native Burmese and worked in The Republic of the Union of Myanmar. Since I graduated from University of Medicine (2), Yangon at 2010, I have been working the most of my career time in the public health sector especially in communicable diseases such as HIV/STI and TB/MDR-TB. Throughout my eight years working period, I have always worked in the Senior Management level, program management sector in the international NGO, local NGO and Civil Society Organizations (CSOs) through community-based projects even including special administrative region and hard-to-reach areas.

In Myanmar, TB is still one of the major public health problems. Also, it is featuring on the list of "30 high TB burden countries" in the world and it has a high TB prevalence rate with three times higher than the average global rate. Furthermore, it is included in the top 20 countries on the list of 30 high TB/MDR-TB and the list of 30 high TB/HIV burden countries. Therefore, during my work in community health care programs, I realized and ascertained that today millions of people need a handful of public health initiatives and public health in Myanmar is comparatively underdeveloped. There is still so much poverty and suffering and the communicable diseases as well as non-communicable diseases (NCDs) are still a very big burden to the community. Likewise, it is also facing uneven progress of development and the emergence of some forms of communicable diseases such as TB and MDR-TB which become a major public health concern for catastrophic costs.

So far, the health systems and policy management in Myanmar need to be strengthened if we want to achieve the Universal Health Coverage (UHC). Currently, TB/MDR-TB are regarded as one of the nationwide prioritized diseases together with HIV/AIDS and Malaria to urgent control in National Health Plan (NHP). Although the case detection rate and treatment success rate (TSR) are significantly improved compared to previous decades, it still poses a threat to the programmatic management of drug-resistant TB (PMDT) activities of NTP.

According to the need of the country's situation and regarding my specialized professional area, I chose the thesis topic related to MDR-TB. This study was inspired by the research for QOL and HRQOL of MDR-TB patients and its applicability to MDR-TB patients living in Yangon Region, Myanmar. This study intends to explore which are the most likely factors influencing the QOL of MDR-TB patients and its impacts or effects on the patients' HRQOL to make recommendations to NTP and MoHS to properly address the problems faced by MDR-TB patients and to improve the QOL of the patients living in Yangon, Myanmar. A better understanding of patients' related QOL may help the health care authorities to ensure adequate and effective management of TB control activities.

Chapter 1: Background Information

1.1 Aetiology and Situation of Tuberculosis (TB) in the world

TB is a top killer infectious disease, which still includes public health concerns in the global top ten causes of infectious disease-related mortality[5]. The causal agent for TB infection is ***Mycobacterium Tuberculosis*** which mainly has effects on lungs as pulmonary TB (PTB) by airborne transmission[6] and it can also affect any society, there is no free TB space in the world[6]. The Global TB report, 2018 by the World Health Organization (WHO), stated that the estimated new TB cases were 10.0 million people (range, 9.0 - 11.0 million): 64% and 9% were found in men and people living with HIV (PLHIV) respectively, and approximately one-quarter of the total world population had a latent TB infection (LTBI) in 2017. Almost 90% of TB cases were found in adults ≥ 15 years, so TB can affect adults than children and more men than women (male: female ratio, 2:1)[5,6]. Furthermore, WHO listed "30 high TB burden countries " contributed to 87% of global TB caseload[5].

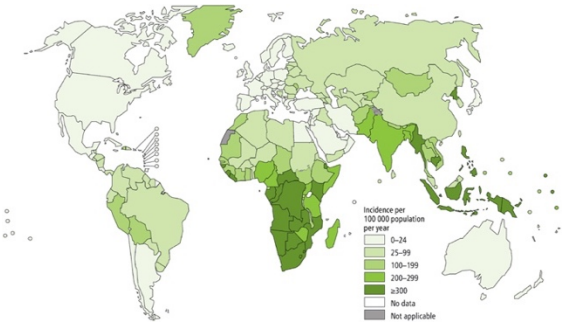
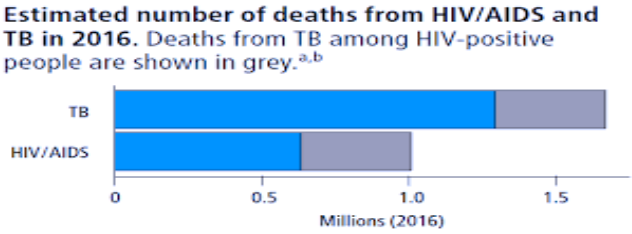


Figure – 1: Estimated global TB incidence rates, 2017[5]



Graph – 1: Estimated number of deaths from HIV/AIDS and TB in 2016[5]

1.2 Types and Classification of TB

There were various classifications of TB[1];

- PTB and extra-pulmonary TB (EPTB) based on the anatomical site of TB infection,
- New patients, previously treated patients and patients with unknown previous TB treatment history based on previous TB treatment history,
- HIV-positive, HIV-negative TB patient and HIV status unknown TB patient based on HIV status.
- Additionally, there were five classifications of drug-resistance TB (DR-TB) depending on the drug susceptibility testing (DST),[1]

Table – 1: Classification of DR-TB depending on drug susceptibility testing (DST)[1]

Monoresistance	resistance to one first-line anti-TB drug only.
Polydrug resistance	resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
Multidrug resistance (MDR)	resistance to at least both isoniazid and rifampicin.
Extensive drug-resistance (XDR)	resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin), in addition to multidrug resistance
Rifampicin resistance (RR)	resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

MDR-TB is a global public health concern, it is needed immediate attention to enhance the effective diagnosis, care, and support for affected patients[5]. TB cases can be diagnosed and bacteriologically confirmed through smear microscopy, culture and WHO-approved rapid molecular diagnostics tests (WRD) such as Gene Xpert MTB/RIF and clinically through history and physical examination by health care providers or by chest X-ray. Although TB or drug-susceptible TB (DSTB) is a curative disease, with 4-first-line anti-TB drugs, by the standard 6-months regimen, nowadays, the emergence of drug-resistant bacterial strains has been noted in many situations. According to 2018 Global TB report, MDR-TB occurrence rate was "3.5% of new TB cases and 18% of previously treated TB cases" globally [4–10].

"Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the two most powerful, first-line anti-TB drugs"[6]. MDR-TB can be regarded as a form of acquired TB, so Gene Xpert MTB/RIF and culture are widely used for diagnosis of this disease. Though it is a curable disease, the limited treatment options and extensive treatment duration, with toxic drugs, poses a crisis in the public health sector and challenges the global TB control activities in 2017 and about "8.5% of MDR-TB cases have been noted as XDR-TB"[6] . "XDR-TB is a more serious form of MDR-TB, caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options"[6].

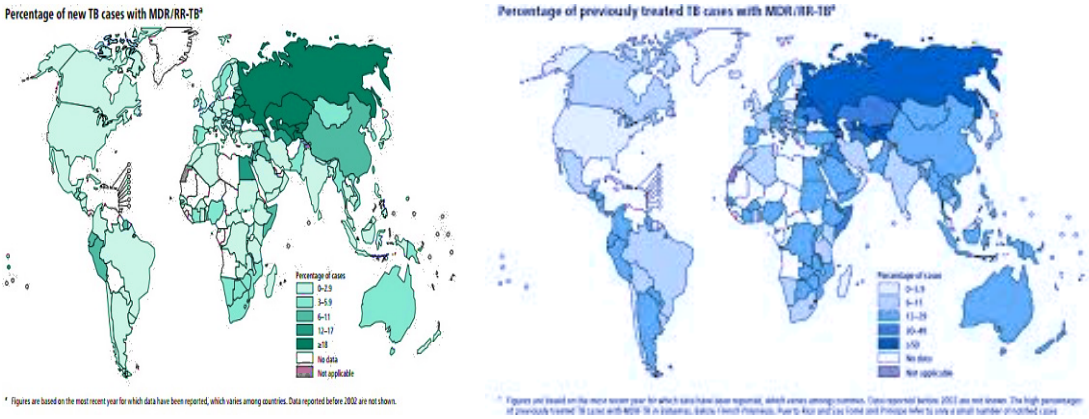


Figure – 2: Percentage of new TB cases with MDR/RR-TB (green) and Percentage of previously treated TB cases with MDR/RR-TB (blue) globally, 2017[5]

1.3 General Risks factors leading to TB and MDR-TB

Although TB and MDR-TB can occur at any age, any sex, and any society, regardless of race and religion, it is associated with many social determinant factors. These are amongst others[2,11];

1.3.1 Individual general characteristics[2,11]

- The male has a higher risk than the female.
- TB can affect people mainly in the productive age (15 – 64 years) but all ages are at risk to get an infection.
- The urban residence has a higher risk than rural, because of more crowded, polluted living and working conditions, but rural people face more health care accessibility problems.
- High-risks individuals: people who have a low immune system and underlying comorbid conditions including HIV, diabetes mellitus (DM), malignancy, malnutrition, extreme ages and pregnancy, history of contact with a primary infected source.
- Individual unhealthy lifestyles: smoking, drugs, and alcohol abuse are attributable risk factors.
- Poor health education, lack of adherence and compliance on treatment, absence of social and family support, stigma and discrimination, psychiatric problems which affect the accessibility to health care services by patients.

1.3.2 Socio-economic and environmental conditions [2,11]

- Poverty and socio-economic inequalities lead to patients' difficulties on proper adherence and they are prone to treatment failure.
- Environmental factors such as crowding, poor ventilation, poor living/ working conditions.

1.3.3 Weakness in the health care management system[2,11]

- Inadequate policies and guidelines for funding, improper functioning of diagnosis and treatment services and management of drug side-effects.
- Insufficient training and low qualified health care workers, lack of qualified health care professionals.
- Lack of health care infrastructure.
- Inappropriate functioning of health care management and information system (HMIS).

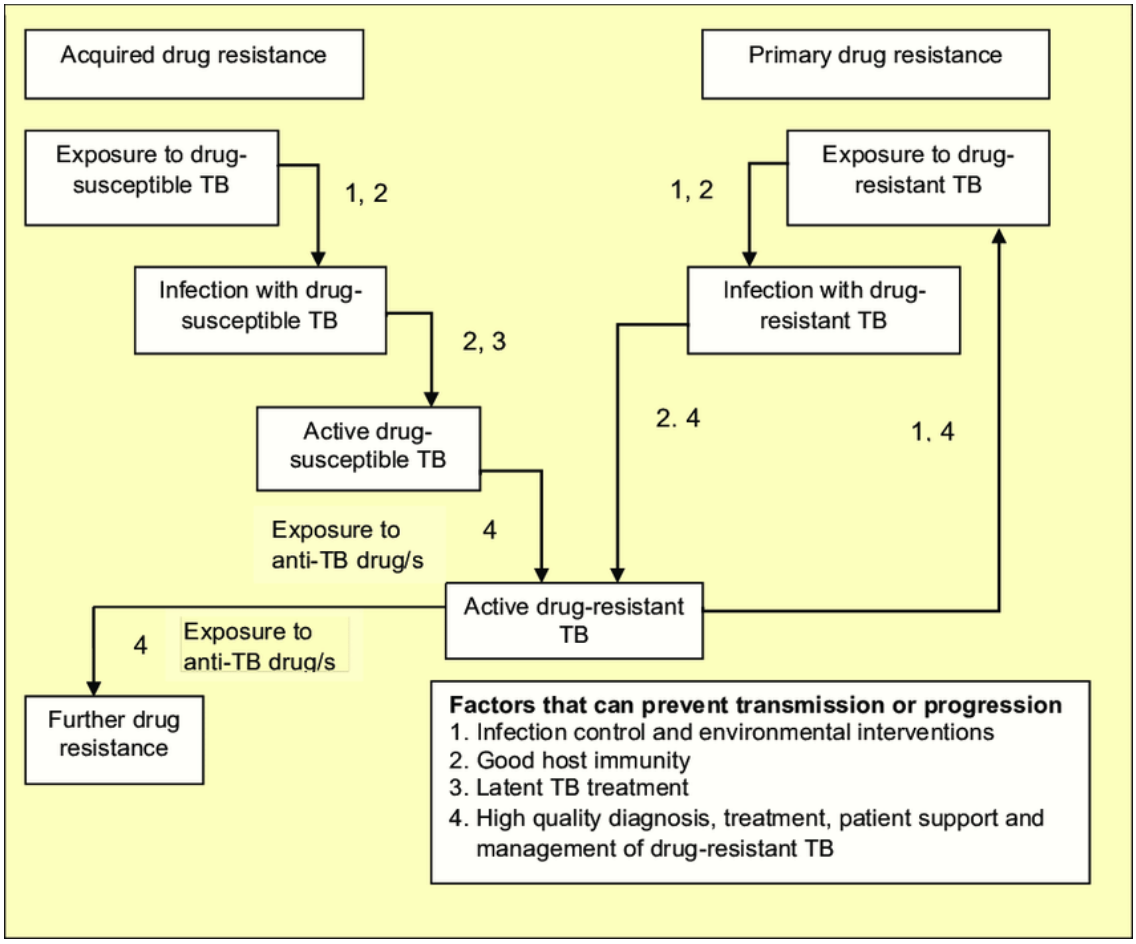


Figure – 3: Two pathways leading to drug-resistant TB (DR-TB)[11]

https://www.researchgate.net/figure/Two-pathways-leading-to-drug-resistant-TB-a-Acquired-Drug-Resistance_fig2_330968488

1.4 Changes in TB Control Strategies overtime

Until 2015, the WHO recommended the complex standard 20-24 months regimen with at least five potent second-line anti-TB drugs for MDR-TB treatment [12], however, the treatment success rate (TSR) is lower than with DSTB of six months regimen[7]. The WHO stated that in 2014, overall TSR was 54% where the mortality rate was 16%, treatment failure was 8% and not evaluated or lost to follow-up was 21%[7]. Therefore, in 2016, the WHO introduced two new drugs Bedaquiline (Bdq) and Delamanid (Dlm), and a 9-12 months shorter treatment regime (STR) for MDR-TB. About 68 countries started to use Bdq and 42 countries used Dlm and about 36 countries practiced STR by the end of 2017[5,7]. Additionally, the treatment-related cost is very high and there is sometimes a need to change or interrupt the treatment due to serious unwanted drug side-effects[4,13]. A majority of MDR-TB related morbidity and mortality, occurred in the South-East Asia Region (SEAR) and Western Pacific Region (WPR) followed by Africa where some countries faced a serious MDR-TB epidemic situation[6,7].

1.5 Demographic and TB Situation in Myanmar

In 2018, World Bank data described Myanmar as a lower-middle-income country in SEAR with a 676.6 square kilometres surface area, 17 states and regions, one Union territory, 69 districts, and 336 townships. It also had a 53.71 million population, 71.21 billion Gross Domestic Product (GDP) and a life expectancy at birth of 66.7 years[14]. Also, it is featuring on the list of 22 "high TB burden countries" in the world and it has a TB prevalence rate, three times higher than the average global rate. Moreover, it is included in the list of 30 high TB and MDR-TB and also 30 high TB/HIV burden countries (Figure – 4)[5,11]. XDR-TB cases were noted since 2007 in Myanmar[4] so TB and MDR-TB are listed as a prioritized disease and a country-wide public health concern in the National Strategic Plan (NSP, 2011 – 2015 and 2016-2020)[11].

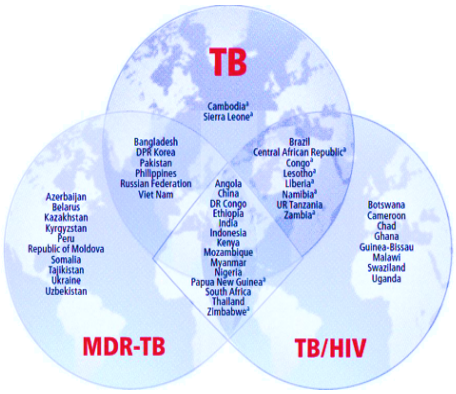
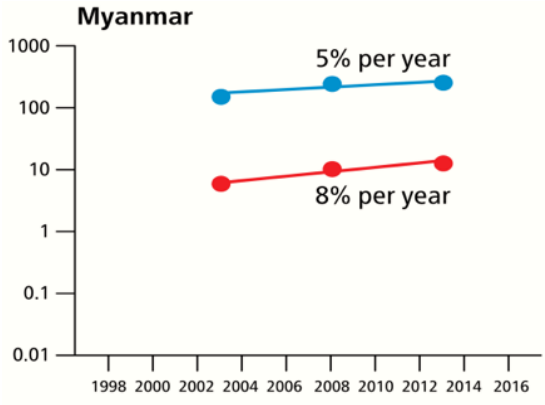


Figure – 4, Countries in the three high-burden country lists for TB, TB/HIV, and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap[5]

1.6 TB Burden in Yangon Region

Yangon region, which is a former capital city of Myanmar, is comprised of 45 townships,[15] it has the largest diverse 7.3 million population and it contributes one-fifth of the country's economy[16]. Due to crowded and migrant populations, old governmental buildings, improper infection controls, under-diagnosis and underreporting, it is regarded as the MDR-TB crisis area[4]. In 2016, Yangon contributed to the highest MDR-TB caseload 1,364 among the total of 2,544 in the whole country[17] and it also had the highest contribution among total 9,133 MDR-TB patients cumulatively enrolled between 2009 and 2017 in the whole country (Annex – 1, 2)[18].



Graph - 2, Trend in the number of new notified MDR-TB cases per 100,000 population (blue) and the number of MDR-TB cases among new TB patients per 100 000 population (red). WHO, Global TB report 2018.[5].

1.7 Programmatic Management of DR-TB (PMDT) in Myanmar

Under the guidance of the "Ministry of Health and Sports (MoHS), Myanmar", the National Tuberculosis Control Program (NTP) vertically manages to TB control activities in country-wide decentralization approach[17], even township level through integration with Primary Health Care[17]. Since 2009, NTP implemented PMDT through Direct Observed Treatment, short course (DOTS), patient-centred approach and Community-based TB Care (CBTBC) activities started at 2011 [17] along with the utilization of Gene X-pert MTB/RIF machines.[19,20] NTP set up 48 machines in the whole country by the end of 2015[19]. Since 2016, NTP started treatment with the new drugs Bdq and Dlm in selected 26 patients and adopted STR in 200 patients, through a pilot project in October 2017[18].

Chapter 2: Problem Statement, Justification, Objectives and Methodology

2.1 Problem Statement

Myanmar has important long-term DR problems and the two country-wide DR surveys, for the MDR-TB occurrence rate, have been implemented by NTP. The results were "4% in new cases and 15.5% in previously treated cases" at 2002-2003 and "4.2% in new and 10.0% in previously treated cases" in 2007-2008 respectively[21]. In the third country-wide survey in 2008-2013, the MDR-TB occurrence rate increased up to "5.1% in new TB cases and 27% in previously treated cases"[19]. Therefore, Myanmar has a higher MDR-TB occurrence rate compared to the 2018 global average of "3.5% in new and 18% in previously treated TB cases" [4,5,22]. Regarding the MDR-TB crisis, the Yangon area has 10% MDR-TB rate among new cases, which was nearly two times higher than the national rate of 5.1%. Therefore, people who live in Yangon had a two times higher risk to get the MDR-TB infection, compared to other states and regions[4]. Throughout these periods, the country is increasing its efforts and is increasing the enrolment of treatment, but unfortunately, the MDR-TB occurrence rate steadily increased in spite of those efforts. The WHO estimated that nearly 132,025 people were notified as TB, among them 8,700 were infected with MDR-TB in Myanmar in 2017 (Table – 2). [23]

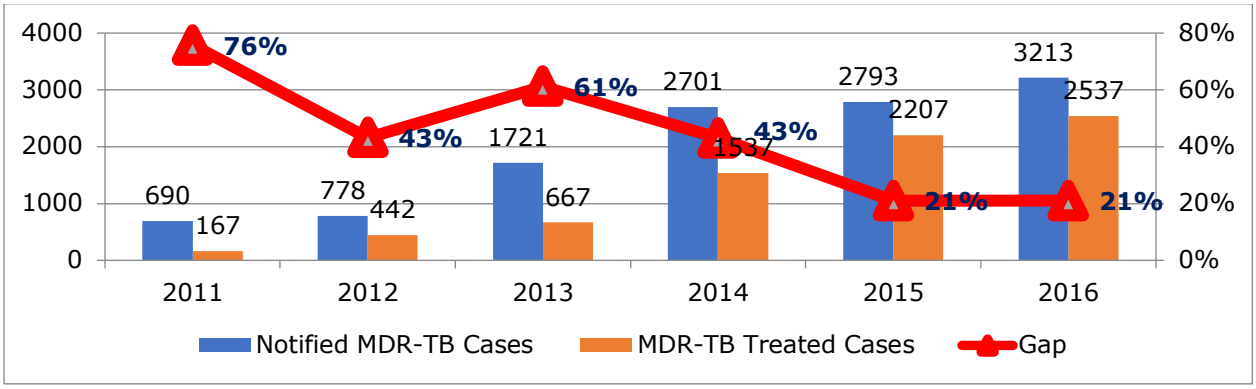
Table-2: The World Health Organization. Country Tuberculosis Profile, Myanmar. 2017[23]

Drug-resistant TB care, 2017	New cases	Previously treated cases	Total number***
Estimated MDR/RR-TB cases among notified pulmonary TB cases		8 700 (6 200–11 000)	
Estimated % of TB cases with MDR/RR-TB	5.1% (3.4–7.2)	27% (16–40)	
% notified tested for rifampicin resistance	29%	63%	43 548
MDR/RR-TB cases tested for resistance to second-line drugs			165
Laboratory-confirmed cases		MDR/RR-TB: 3 281, XDR-TB: 28	
Patients started on treatment ****		MDR/RR-TB: 2 666, XDR-TB: 9	

While 2,537 patients enrolled in 2016 for MDR-TB treatment, which was 15% higher than compared with 2015 (2,207), there was still a gap of missing cases to enrol all MDR-TB notified cases (3,213) on treatment for 2016, in spite of the increased case notification and enrolment[18]. There was a delay in accessing diagnosis and treatment

due to a lack of the patients' awareness, low health education, stigma and discrimination by societies[24,25].

Graph – 3: Year-wise RR-TB notified, enrolled in DR-TB regimen and the gaps, Myanmar[18]



MDR-TB itself is a socio-economic related disease and it affects the poor and impoverished population, especially with low socio-economic status (SES). Most of the patients face a loss of productivity, loss of income due to being unable to work and the sense of identity. Also, the psychological, social and economic burden which is aggravated by the consequences such as the drug side-effects, the catastrophic costs, stigma and discrimination from family, friends and their communities. Consequently, the majority of patients suffer a low quality of life (QOL) in terms of physical and psychological well-being, personal and social relationships[4,26].

2.2 Quality of Life (QOL) Aspect

The worldwide TB control programs pay a lot of attention to improve the quality of care (QOC) services and long-term QOL of patients, according to the WHO-QOL definition as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" [27,28]. "Considering the health-related QOL (HRQOL), which is multi-dimensional, all-inclusive assessments of the patient's health and well-being was important, despite clinical and physical assessments of MDR-TB patients". Taking into account, the overall impact of TB, MDR-TB on the patient's health status, patients' views and perceptions related to their QOL, through several domains were needed[29]. Also, the family and social support was important and had an influence on the patients' drug adherence and successful treatment, which in turn improved the QOL of those patients in the future [4].

2.3 Justification

Nonetheless, the majority of the TB control activities and research studies were mainly focusing on clinical and treatment-related sectors, so the patients' perceptions of the HRQOL are still needed to be explored[30,31]. Even in the developed countries, the studies and papers, for the impacts and effects of TB and MDR-TB on QOL of patients, were scant and undervalued [32]. Not surprisingly, there was a lack of sufficient evidence-based studies related to QOL of TB and MDR-TB patients in developing countries [32,33]. Yet the QOL was an important factor, defining whether or not a patient can and wants to complete treatment. Therefore apart from a moral obligation, to offer the patients support during their treatment, QOL should take into account, which parts contribute to the value and performance of NTP's implementing TB, MDR-TB prevention and control

activities[33]. A better understanding of patients' HRQOL may help the health care authorities to ensure adequate and effective management of TB control activities.

Currently, the country has a national-level commitment to Sustainable Development Goals (SDGs) and END-TB strategy by 2035. By 2020, the country's NSP prioritized to enrol all MDR-TB patients into treatment within two weeks after getting their diagnosis through patient-centred and comprehensive approach,[18,34] including social support, that considers human rights and the patients themselves, to be a part of a social network and a sense of responsibility (Annex – 3,4, Figure – 5, 6)[3,34]. Besides, the country is on the way towards Universal Health Coverage (UHC) and social protection according to the WHO recommendation, by eliminating the financial hardship and disease-related catastrophic costs, which impacts on social and public health[35]. Therefore, NTP and MoHS need to carry out the effective management in TB, MDR-TB related services and strengthen the capacity to support comprehensive health care services for improving the QOL of beneficiaries to achieve its goals and objectives.

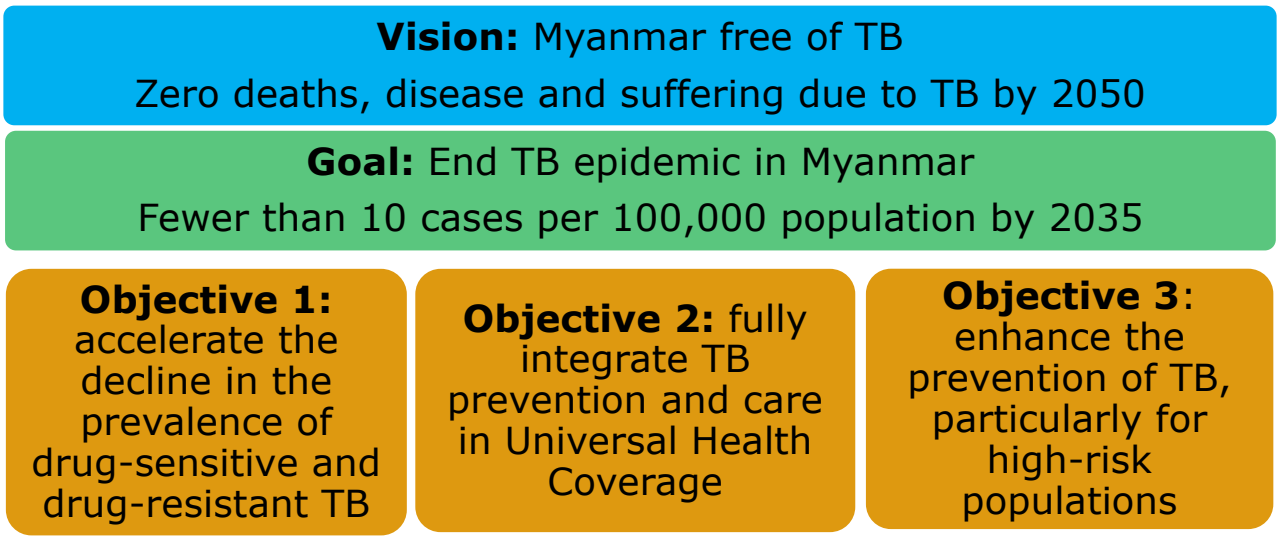


Figure – 5: Vision, Goal, and Objectives on Ending TB in National Strategic Plan, Myanmar[34]

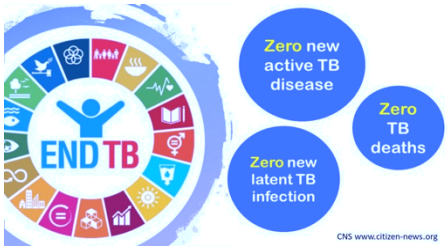


Figure – 6: END-TB Strategy, World Health Organization[36]
http://www.asiantribune.com/sites/asiantribune.com/files/images/2012/Zero%20TB%20infection%20and%20zero%20deaths.jpg

Myanmar has recognized the need for better understanding of QOL aspects and plans to do an in-depth national-level study, related to MDR-TB management soon, but there are inadequate studies until now. To understand and study all of these factors, related to QOL, further operational researches are needed. Therefore, it was very important and it

was needed to conduct the assessment of the factors related to QOL of MDR-TB patients living in Myanmar[4]. In the implementation of PMDT activities, there is a need to cover, during the whole treatment period, to understand the impacts of QOL. Therefore, the present study aims to explore the factors influencing the QOL and HRQOL of MDR-TB patients and its applicability to MDR-TB patients living in Myanmar, to make recommendations to health care authorities including MoHS, NTP and all stakeholders. This literature review may act as a basis for developing such a study and may already give clues as to interventions which can be piloted to improve the MDR-TB patient's QOL through effective TB and MDR-TB control activities in the future.

2.4 Objectives

2.4.1 General Objective: To explore the most likely factors influencing QOL of MDR-TB patients and the impacts of this disease on patients' HRQOL to make recommendations to NTP and MoHS, to address the problems faced by MDR-TB patients properly and to improve the QOL of those patients living in Yangon, Myanmar.

2.4.2 Specific Objectives

2.4.2.1 To understand how MDR-TB disease and its treatment impacts QOL domains (physical health, psychological health, social relationships, and environment) of affected patients.

2.4.2.2 To explore if and to what extent individual characteristics of patients (such as age, sex, education, income, employment, and living circumstances) aggravate or are protective against the effect of MDR-TB on QOL.

2.4.2.3 To identify how illness-related factors (symptoms, treatment-related adverse drugs reaction (ADRs), patients' beliefs and perceptions on their illness) affect the QOL of MDR-TB patients.

2.4.2.4 To explore the impacts of social-related factors (including stigma and discrimination, community support, family support, and comprehensive care) on the QOL of MDR-TB patients.

2.4.2.5 To explore how health system-related factors (such as accessibility of health care services, health education, support packages, community-based services, etc) impacts on different domains of QOL of MDR-TB patients.

2.4.2.6 To formulate recommendations to NTP, MoHS to better support MDR-TB patients and improve the QOL of MDR-TB patients living in Yangon, Myanmar.

2.5 Conceptual framework

The conceptual framework, presented in this study, was developed based on the mainly WHOQOL-BREF field trial version, complemented by WHOQOL-BREF introduction version and 36-item Short Health Survey (SF-36) instruments (Annexes – 5, 6, 7)[27,37,38]. Previously, the WHOQOL-100 framework focused on the perceived QOL, individual perceived effects related to the disease and treatments, so this cannot be used to measure the detailed disease symptoms and disability. Thus, for convenience assessment of QOL, the WHO further developed the brief version of the assessment of QOL at 1997, namely; the WHOQOL-BREF which comprises 26 items and it covers four domains of physical, psychological, social and environmental aspects (Annex - 5)[37].

The WHOQOL-BREF framework can be used for the generalized QOL of patients in all diseases and it was not specialized to focus on TB and MDR-TB patients. Therefore, developing a conceptual framework of QOL for this study, the researcher used all four

domains to cover all aspects of physical, psychological, social and environment based on the WHOQOL-BREF framework, together with the above mentioned two instruments. Every domain prepared the combination of relevant subscales from the above three reference frameworks to be suitable for the current study's general and specific objectives. For example, in the physical domain, the combination of pain, and daily activities subscales from WHOQOL-BREF field trial, also mobility and daily activities from WHOQOL introduction, vitality and general health from the SF-36 questionnaire. The developed conceptual framework in this study can be seen as follow; MDR-TB and its treatment have impacts or effects on the four domains of QOL of infected patients namely physical, psychological, social and environmental domains as shown in the right side of the framework. On the left side the framework depicts a number of factors such as personal characteristics, illness-related effects, social factors, and health system-related factors can influence the severity of the impact on QOL either as factor worsening the effect or being protective and mitigating the impact of the disease and treatment on people's life (Figure – 8). Understanding these predisposing or mitigating factors provide clues on how best to support patients.

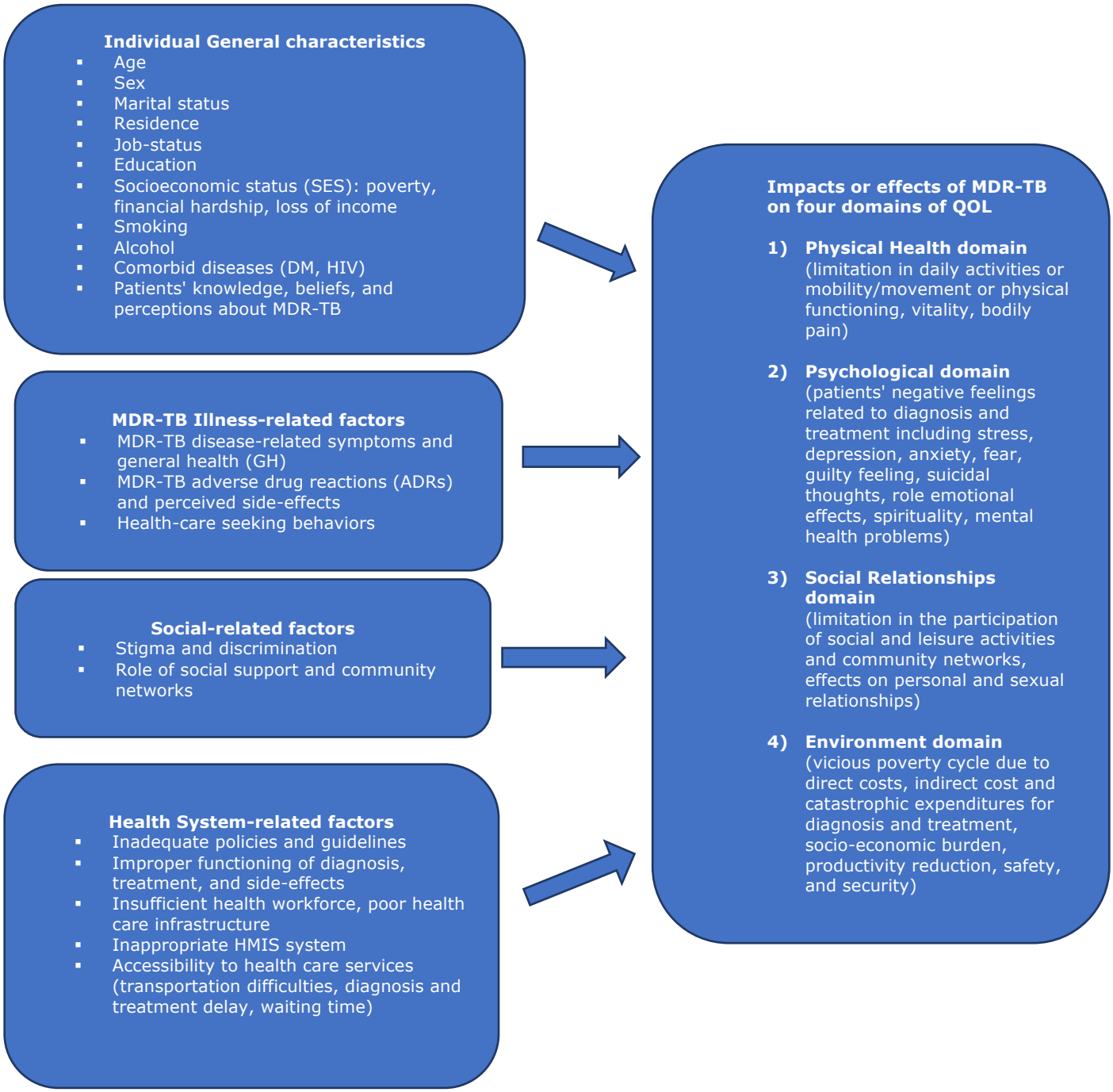


Figure – 7: Conceptual Framework to assess the Factors Influencing on QOL/HRQOL and its Impacts on MDR-TB patients

2.6 Methodology

This study was carried out mainly as a systematic literature review by desk study. A comprehensive search strategy resulted in a narrative literature review. The primary literature was searched to look for peer-reviewed articles, journal articles, and papers by browsing search engines such as Google, Google Scholar, US National Library of Medicine (NCBI), Baseboard Management Controller (BMC), Public Library of Science (PLOS), online Burma Library and a free online library of Vrije Universiteit Amsterdam

(VU). Also, through the search of the PubMed Central databases (PMC) and reports from the WHO, Myanmar NTP reports, Medical journals and Grey literature. Using the snowball approach for the secondary search, according to the reference lists of the primary search. The literature was searched based on the set criteria of inclusion and exclusion (Table -3).

Table – 3: Inclusion and Exclusion criteria

Inclusion criteria	This study mainly focused on the studies that researched the effects of TB and MDRT-TB on QOL or HRQOL and the factors contributing to improve or deteriorate QOL or HRQOL of TB/MDR-TB patients. The types of studies included both qualitative and quantitative studies including prospective and retrospective cohort studies, case-control studies, comparative studies of determinants, longitudinal studies, exploratory and cross-sectional studies, systematic review articles exploring the influence of TB and MDR-TB on people's life and research factors that contributed positively or negatively on the QOL or HRQOL of TB/MDR-TB patients. The study limited the literature published within the period between 1990 and 2019, because of the TB and MDR-TB treatment guideline always update, change and the WHO recommended practicing patient-centred approach based on DOTS strategy, the END-TB strategy and SDGs were mainly developed within these periods. The literature review mainly focused on Myanmar and similar context like the low- and middle-income countries with high TB, the MDR-TB burden. The main language used for searching was English.
Exclusion criteria	Excluded were articles which were not directly or indirectly related to TB, MDR-TB, QOL, and HRQOL and not relevant to apply in this study. The articles which full-text view was not accessible to viewers and publications are written in a language other than English were excluded.

Terms included in the search strategy were related to the concepts of QOL based on the Conceptual Framework such as the Mesh terms or other associated terms (Annex – 8, Table - 4).

Table – 4: _Searched Term used

		AND	OR	OR
OR	TB MDR-TB	QOL HRQOL Impacts Effects	Physical impacts Psychological impacts Social impacts Environmental impacts Illness-related factors Disease-related symptoms Diagnosis and Treatment Drug adherence Drug side-effects Adverse Drug reactions Psychological consequences Perceived perceptions Stigma Discrimination Perceived stigma Social support Community networks Environmental factors Socio-economic conditions Financial impacts Poverty Education Age Sex Residence Employment Smoking Comorbid diseases	Low or middle-income countries high TB, MDR-TB burden countries Myanmar

Once the key papers were identified, the researcher reviewed key themes particularly related to the WHOQOL four domains; physical, psychological, social and environmental aspects. All the relevant retrieved articles were exported to the Mendeley Reference Manager for referencing.

Chapter 3: Results and Findings and discussions

The results and findings were extracted from reviewing the literature and related articles, then analysed according to the above QOL conceptual framework. Although the majority of the results and findings focussed on the factor influencing all form of TB and its impacts on QOL, but MDR-TB is also a man-made or an acquired disease from the continuation of TB, thus, it has almost the same aetiology, presenting signs and symptoms, negative consequences on the patients' QOL. A few differences are; MDR-TB needs long-term treatment with more severe drug side-effects and complications than

TB. Therefore, the researcher used all the articles and literature about QOL related to TB and MDR-TB then drew appropriate conclusions for recommendations as per set objectives (Annex – 9).

There were varieties of instruments to measure the QOL, among them the WHOQOL-BREF framework, SF-8, SF-12, and SF-36 instruments were widely used by many researchers (Annex – 10)[39]. In this paper, the searched studies were mostly cross-sectional, cohort, case-control, longitudinal and sometimes mix-methods in nature and the findings were presented as different types of QOL scoring and subscales based on the preference of the original researchers as follows,

- Four domains: physical health, psychological health, social relationships, and environment mainly stated in the studies using WHOQOL-BREF.
- Two components: physical component summary (PCS) and mental component summary (MCS).
- Two dimensions:
  Dimension A - physical health {physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), and vitality (VT)} and
  Dimension B – mental health {GH, VT, social functioning (SF), Role Emotional (RE) and mental health (MH)} especially found in the studies used by SF-36 instruments.

3.1 Main findings on Illness-related factors and Impacts or Effects of MDR-TB on all QOL domains

Albeit the QOL four domains were independently mentioned in the WHOQOL-BREF framework, the numerous articles and literature showed comparison or interrelation between the domains.

Firstly, the Darvishpoor's study, for the evaluation of the factors associated with HRQOL in 205 TB patients from National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran through SF-36 was carried out at December 2013 to March 2014[33]. Not surprisingly, HRQOL scores in TB patients were noteworthy lower than the general population, the role limitation (RL) was the lowest score affected by emotional distress (mean ± standard deviation [SD], 14.68 ± 11.60) while the highest score found in GH (mean ± SD, 46.99 ± 13.25) (Table – 5)[33]. The results confirmed that the physical health domain was the most affected area, in addition, the various general characteristics, such as education, employment status, individual lifestyle and sociodemographic factors were also affected in different domains of QOL[33]. Findings of the Sharma's study[29] were similar showed more severe impacts on all four domains of QOL in MDR-TB than PTB controls.

Table – 5**:** Means for eight subscales of SF-36: Iranian version of the 36-item Short-Form Health Survey, Tehran[33]

Dimension	Mean ± SD
Physical functioning	39.97±25.84
Role limitations due to physical problems	19.77±9.14
Body pain	30.80±26.58
General health perceptions	46.99±13.25
Vitality	24.19±15.40
Social functioning	40.01±17.52
Role limitations due to emotional problems	14.68±11.60
Mental health	30.91±8.02

https://doi.org/10.4046/trd.2015.78.4.309

According to the analysed study of the MDR-TB impacts on QOL of each 60 samples PTB and

MDR-TB cases in North India, the findings clearly described that both TB and MDR-TB had negative impacts on QOL of patients, MDR-TB individuals were more hampered than the former group[29]. The average scores were significant in all domains and the overall QOL between them (mean difference MDR-TB 6.83; PTB 4.81). Compared to the control group, the scores of PTB patients showed remarkable better than MDR-TB patients especially in psychological and environmental domains (MDRTB vs PTB, 15.23 vs 17.46 and 18.91 vs 22.00) apart from the physical and social domain (19.03 vs 20.05 and 7.88 vs 9.61) (Table- 6)[29]. MDR-TB patients suffered more financial burden than their counterparts and SF impairment due to lack of family and community support[29]. Sharma's findings were different from Tehran,[33] the physical health was less hurt than other domains and psychological distress, safety and security, living and working conditions were also affected[29].

Table – 6: Mean table for the impacts of MDR-TB on all QOL domains compared to controls, North India [29]

	MDR Mean	Anti-tuberculosis treatment (ATT) Mean	Control Mean	F-Ratio
Domain- I Physical Health	19.03	20.05	24.08	28.902**
Domain- II Psychological	15.23	17.46	22.35	49.201**
Domain-III Social Relationship	7.88	9.61	12.45	28.837**
Domain-IV Environment	18.91	22.0	29.5	65.311**

In Hamadan, Western Iran, Mamani conducted a cross-sectional study for QOL assessment in 64 TB cases and 120 controls, who were being on treatment between 2009 - 2011 via SF-36. The cases group's overall score was significantly lower than the control ($p<0.001$) at baseline and the lowest scores were found in energy (44 ± 22 vs 63 ± 21) and GH (49 ± 19 vs 68± 17) (Table – 7)[40]. With the follow-up measurements, after two and six months, the scores steadily improved throughout the treatment, but there was no significant difference between two and six months. Although the scores improvement could be seen, the overall QOL score, after treatment completion, remained lower than in the general population mainly due to psychological effects[40] .

Table – 7: Comparison of eight SF-36 category scores between the TB patients and the control group in Hamadan[40]

SF-36 category	Score		*p*-value
	TB patients (N=64)	Control (N=120)	
Physical functioning	65 ± 28	78 ± 26	0.003
Role functioning	45 ± 42	71 ± 35	<0.001
Bodily pain	58 ± 33	73 ± 25	0.01
General health	49 ± 19	68 ± 17	<0.001
Energy	44 ± 2 4	63 ± 21	<0.001
Social functioning	60 ± 27	75 ± 22	<0.001
Health perceptions	52 ± 43	70 ± 37	0.006
Mental health	52 ± 20	66 ± 21	<0.001
Total score (QOL)	54 ± 20	71 ± 18	<0.00

Louw J, et.al conducted a cross-sectional study to investigate HRQOL in 4,900 TB, previously treated TB and TB/HIV coinfected patients, from the primary health care clinics in South Africa through SF-12. The overall findings described PCS and MCS scores as 40.7 and 42.5 respectively, in which the MH domain had the highest score together with the lack of energy and fatigue and GH, BP along with emotion, got the lowest scores (Table – 8)[41]. According to a multivariate analysis result, the amazing point was found that education, low psychiatric problems, less comorbid conditions, in HIV negative individuals, had a positive association with PCS while less poverty and psychological problems in HIV positive, were positively associated with MCS, but the results did not show any differences between age and gender. The comorbid conditions could lead to significantly lower QOL scores in coinfected patients, than the TB patients without HIV except MCS, RE, VT, MH, SF and RP[41].

Table – 8: SF-12 health survey scale means for patients with active TB infected with HIV and without HIV, South Africa [41]

SF-12 Subscale	TB-HIV infection	TB without HIV	P-value	Total sample
	Mean (SD)	**Mean (SD)**		**Mean (SD)**
General health (GH)	35.5 (12.6)	42.6 (13.4)	0.000	38.5 (13.4)
Bodily Pain (BP)	38.5 (11.8)	40.2 (11.8)	0.000	39.2 (11.9)
Physical Function (PF)	40.5 (11.2)	41.4 (10.7)	0.027	40.9 (11.1)
Physical Role (RP)	40.9 (9.2)	39.8 (9.6)	0.000	40.5 (9.4)
Social Function (SF)	41.0 (11.7)	39.3 (13.0)	0.000	40.5 (12.2)
Mental Health (MH)	43.1 (9.5)	40.6 (10.5)	0.000	42.2 (10.0)
Energy and Fatigue (Vitality) (VT)	49.8 (10.7)	46.3 (11.3)	0.000	48.3 (11.1)
Emotional role (RE)	37.6 (11.1)	36.3 (12.1)	0.000	37.3 (11.5)
SF-12				
Physical Health (PCS)	39.6 (9.2)	42.5 (8.4)	0.000	40.7 (9.1)
Mental Health (MCS)	43.7 (9.7)	40.4 (11.4)	0.000	42.5 (10.5)

The MSF clinic and Jupitar Hospital Mumbi, a cross-sectional study was conducted with 107 DR-TB patients for assessment of HRQOL. The results were, the most affected in psychological domain succeeded by physical (56.2, SD 18.3 and 56.6, SD 15.1)[42]. Social and environment were 68.6 (SD 621.1) and 60.3 (SD 615.9) respectively. Other predictors of job status, drugs side-effects, psychological distress, fear and stigmatization also affected the QOL domains. Also, the supportive role of health care provider, family and working condition were a part of important themes in improving QOL[42] . Another cross-sectional study in India, conducted by Apoorva E, et.al amongst 52 MDR-TB patients, compared to 53 non-MDRTB and 54 cured DSTB patients who enrolled during January 2013 – June 2014 through WHOQOL-BREF[43]. The QOL of MDR-TB cases were more severely affected than non-MDRTB patients (physical domain and environmental domain, $p<0.001$) as well as (physical and psychological, $p<0.001$) lower than cured DSTB patients. Thus, the most affected area was the physical domain even TB had a negative impact on patients' QOL but worse in MDR-TB patients (Table – 8)[43] . There were the agreement between the most and

second most affected domain was physical health in the studies of (33,40,41,43) and the psychological was more affected than physical health found in (29,42) studies.

Table – 9: Comparison of QOL scores (transformed scores) among the study subjects in different domains, India[43]

Domains	Median (IQR)			P-value
	MDR-TB (N=52)	Non MDR-TB (N=53)	TB cured (N=54)	
Physical	39.3 [25.0-56.3]	53.5 [39.3-64.3]	89.3 [82.1-96.4]	<0.001
Psychological	50.00 [38.5-62.5]	54.2 [50.0-66.7]	87.5 [79.2-95.8]	<0.001
Social	75.0 [66.7-75.0]	66.7 [58.3-75.0]	62.5 [50.0-75.0]	0.11
Environmental	65.6 [60.2-75.0]	75.0 [70.3-82.8]	62.5 [53.1-81.3]	<0.001
*Kruskal Wallis test. P<0.05 is considered statistically significant.				

Further 62 Pilipino MDR-TB patients diagnosed at January 2013 – April 2015 were analysed by a cross-sectional study using the WHOQOL-BREF, found that the MDR-TB disease and its treatment had both direct and indirect impacts on QOL[44]. All domains scores were higher among young males with a high SES, high income, well-educated who were taking on STR. The physical health was the most suffered domain, affecting independence level, daily activities, BP, discomfort, mobility and ability to work whereas the environment was the least affected one[44] . The China's HRQOL study certified again that the fact of physical health was the most hampered area in 102 TB patients compared to 103 controls. The BP was the strongest predictor of low QOL because it was the most affected one as well as the most rapid responded to anti-TB drugs[45]. In February to July 2017, the HRQOL assessment study was carried out in Eastern Ethiopia, the findings were differed from above studies, the physical domain had no significant difference between a total of 100 MDR-TB cases and 300 DSTB controls through SF-36v2 TM (57.61±16.42 and 59.13±22.10). But, GH had the worst score and BP was lesser in MDR-TB cases [46] . Also, another different finding from Apoorva E, et.al,[43] stated that the physical health was the second most affected domain (56.5 ± SD 15.1) along with the symptoms of generalized weakness, nausea, headaches, vomiting, limitation in movement, numbness, tingling sensation and BP .

A Namibian cross-sectional study, administered in 36 MDR-TB patients, who completed treatment using SF-8. The overall median PCS score was 58.6 (range 35.3 – 60.5): the highest scores in BP, GH, and VT whereas the poorest scores in PF, RP, and RE which shifted to low QOL, but, the only interesting point was that the adverse drug reactions (ADRs) did not impose to low QOL scores in that study[47]. Another descriptive study investigated the impacts of MDR-TB on Indian patients' QOL who were being completed in 6-months anti-TB treatment before March 2015 through WHOQOL-BREF. Male patients had higher mean scores in all domains than female (Table – 10). In this study, the social domain got the lowest scores in both sexes, therefore, personal and sexual relationships, and social participation in networks were severely affected[48].

Table – 10: The Gender distribution of MDR-TB patients' QOL in three districts of India(48)

Domains	Physical Mean (SD)	Psychological Mean (SD)	Social Mean(SD)	Environmental Mean (SD)
Male	55.4289(12.10)	54.6395(13.09)	52.4035(18.14)	58.4072(16.21)
Female	53.1131(13.25)	52.6961(12.35)	47.6827(19.18)	56.9853(16.86)

The dissimilar findings concluded in Adeyeye's Nigerian study, that both male and female were non-significant equally affected on physical and environmental, because females had comparatively better scores in psychological and social domain than their male

counterparts[49]. The lowest score in the environmental domain and the income, illness duration, age and job status were the important predictors for that study[49].

A prospective Delhi's HRQOL study mentioned that the TB cases had significantly lower mean scores in overall QOL domains, than general population controls, however, the physical and psychological domains had the lowest score (9.32±1.73, 9.82±1.98) among all domains (Table – 10)[50]. Assessment after three months and after treatment completion, the overall QOL scores of cases considerably improved, the greatest improvement was in the physical domain. There was a difference in the overall QOL scores between male and female, the female possessed an overall lower score but their physical score was better than the male[50] .

Table – 11: Mean QOL scores by QOL domains, Delhi[50]

Domain	Physical Mean (SD)	Psychological Mean (SD)	Social Mean (SD)	Environmental (SD)	Overall QOL Mean (SD)
Cases *N* = 90	9.32 (1.73)	9.82(1.98)	14.35 (2.50)	11.43(1.61)	10.98(1.40)
Controls *N*= 90	12.11 (0.91)	13.08(1.37)	15.68(1.74)	14.03(1.23)	14.21 (1.00)
Mean difference	2.79	3.26	1.33	2.60	3.23
t-value	15.11	12.84	4.12	12.13	15.45
P-value	0.000	0.000	0.000	0.000	0.000

According to a review of specific studies, the environmental domain was the least affected area among all domains this was confirmed by Kaya's study, the disease and its treatment severely affected all QOL domains but relatively spared the environment [44]. Although the physical domain was the most affected, on the other side it was a great improvement during treatment, this findings was common in (44,45,50) studies.

3.2 Differentiated effect on QOL by Individual General Characteristics and SES

Considering the QOL in MDR-TB patients, which mainly occurred in poor, marginalized and low SES population. Then the disease itself, its treatment and side-effects had both direct and indirect negative impacts on the patient' socio-economic and financial situation. Therefore, MDR-TB and SES interrelated with each other like a poverty vicious cycle.

In North India, the quantitative assessment of HRQOL was carried out in 1,034 PTB patients using the WHOQOL-BREF Hindi's version at three occasions: treatment initiation, after intensive phase and treatment completion. Generally, all scores in young males, living in urban situation, these had high SES with less severe disease-related symptoms were better than the old-aged, rural patients with severe symptoms and low SES[51]. This fact was complemented by Darvishpoor's study,[33] the rural residents had lower scores in physical health than their urban counterparts, due to the limitations in daily PF and BP. Not only this, but also the psychological, social and environment scores, were affected by general characteristics, such as sex, smoking, marital and job status. A great difference was seen in RL, VT and socioeconomic well-being scores between patients who had jobs and retired persons, unemployment and retired persons and house-keeper and retired individuals[33].

Table – 12: SF-36: Iranian version of the 36-item Short-Form Health Survey[33]
https://doi.org/10.4046/trd.2015.78.4.309

	Physical functioning	Role limitations due to physical problems	Bodily pain	General health perceptions	Vitality	Social functioning	Role limitations due to emotional problems	Mental health
Marital status				P=0.001				
Single				50.27				
Married				46.69				
Divorced				33.00				
Educational level	P=0.000	P=0.000	P=0.018		P=0.000			
Illiterate	34.31	14.34	27.10		19.58			
Primary and high school	54.25	21.81	37.67		35.49			
Job status		P=0.003			P=0.002			
Employed		15.18			30.92			
Unemployed		21.55			20.44			
House-keeper		20.88			23.96			
Retired		22.08			20.35			
Residence	P=0.014	P=0.046	P=0.000				P=0.003	
Town	41.78	19.16	33.89				13.47	
Village	33.21	21.95	19.99				18.99	
Cigarette smoking						P=0.027		
Non-smoker						41.31		
Smoker						33.33		

Equal findings from the Myanmar cross-sectional study, amongst 210 PTB patients, was conducted in May to November, 2017, the rural settlers got significant low scores in the physical health domain due to BP and RL, but the urban people suffered more emotional distress due to stigma and discrimination from the communities which all drove the serious impacts on QOL [20]. Additionally, some poor and marginalized patients encountered social problems because they were breadwinners of their family so they could not leave their jobs although they got the disease. No doubt, those people suffered financial ruin and debts which led to the deep poverty cycle[20].

A prospective study in Penang General Hospital, Malaysia, was carried out in 216 new smears positive PTB patients, who were registered between March 2010 – February 2011 through SF-36v2. The overall PCS and MCS scores showed predictive differences in general characteristics, smoking and income status [31]. Likewise, in South Africa's longitudinal study, administered to a total of 131 TB patients in primary health care centres at November 2014 – May 2015. The HRQOL in all domains were impaired at the baseline level, especially more suffered in low-educated old-aged, jobless patients than in well-educated younger ones. The significant impacts of age and gender on QOL of patients could be observed, also education and job status too[52]. Through Adeyeye's study,[49] the various sociodemographic predictors, including low income, comorbid conditions, jobless, old-aged, and longer illness duration were related to low QOL scores, while married people were spared the negative impacts than unmarried ones[49] .

An unhealthy lifestyle such as smoking, could affect the individuals' lungs parenchyma and respiratory functions as short-term and long-term impacts on the patients' thoughts, perceptions and physical health. Many people had a negative view on smokers, which impacts on the social relationship and functioning[53] so their HRQOL scores were lower than

non-smokers[32,33,53]. Another unhealthy lifestyle: heavy alcohol drinking/alcohol dependence had a strong relationship with drug-resistance as (OR 8.58; 95% CI 2.09 – 35.32), and relapsed or chronic TB (OR 2.56; 95% CI 1.0 – 6.54) showed in a Russian study during 2002 – 2003[54]. According to those findings, the researcher assumed that an unhealthy lifestyle was one of the risk factors for MDR-TB and patients suffered consequences of disease and treatment, imposed by the negative effects of this, prone to the low QOL score and eventually substantial mortality. Further, in an US-Mexican study, the participants mentioned that they suffered distress or feelings of embarrassment in changing their lifestyle, due to disease and treatment[26] . In contrast to this, Marra CA results from Canadian respondents, highlighted that TB was a "wake-up" sign to change from unhealthy to healthy lifestyles which improved QOL in long-term aspects[55]. So, the similar findings for the association between TB and low SES found in many studies (20,33,44,51,52).

There was strong evidence found in a prospective cohort study, among TB/MDR-TB high burden country in SEAR, Indonesia, during July 2003 – May 2004. The results of 69 notified PTB patients argued that TB had a significant negative impact on the lung function and about 40% of them suffered lung function impairment at treatment initiation[56]. Although anti-TB treatment improved the lung function substantially, a quarter of participants had the residual lung function impairment after treatment completion. Thus, the disability-adjusted life years (DALYs) were still poor along with poor QOL scores[56]. Regarding comorbid conditions, Neves Lis, et.al Brazilian study[28] revealed that TB/HIV coinfected patients had significant lower QOL scores in all domains than HIV patients without coinfection which was similar to Louw J's study findings,[41] therefore, comorbid conditions could pull down the QOL scoring . Depending on the individual general characteristics, each dimension score was different from another[40,57]. Another Brazilian study, from Espírito Santo State, analysed the TB significance in coinfected and pure HIV/AIDS patients during 2000 to 2006. These diseases had well-known interrelated impacts on QOL so the coinfected cases had far poor scores than pure cases, influenced by proxy factors of low education and poverty[58]. With DM, Wita, et.al studied the comparison of QOL between pure DM patients and DM with TB patients in Bandaung city at 2014. The overall score was statistically significant different (58.8 in DM patients vs 53.39 in comorbid patients) and also physical, psychological and environmental domains [59]. It meant that any form of comorbid condition created progressively worse results of QOL.

Although MDR-TB is a form of TB, the impacts on QOL was more severe in MDR-TB patients which was shown in a compare and contrast study from reviewing medical records (during 2008-2013) in Saudi Arabia. The two groups of DR-TB and non-DRTB showed significant differences in terms of global QOL (P=0.000) and global health (P=0.029) respectively[60]. The significant correlation between QOL and socio-demographic factors, including socio-economic, education and employment, could be seen more in DR-TB patients[60]. Dhuria M, et.al[50] mentioned that the overall QOL score in females was relatively lower than males, because TB is related with social and cultural implications which affects more females. Similar findings from the Aggarwal study,[51] it was reported that young males with a higher SES and living in an urban situation had less serious symptoms and better scores than rural female residents.

The structured interview study in Ankara, Turkey, was carried out to discover the association between the differences in sociodemographic factors and QOL in 120 TB patients, who were treated between 2003 and 2004. Confirmed findings, that low SES patients faced financial difficulties, resulted into low scores against high SES patients[61]. Also, low education, lack of social health insurance coverage imposed to negative perceptions about disease and low QOL consequences[61]. Correspondingly, the Tehran study pointed out that patients with a higher income faced a less economic burden and relatively better satisfaction than low socioeconomic patients although both experienced negative disease impacts[33].

Again, one more Nigerian cross-sectional study conducted by the Nigerian Teaching Hospital at December 2010 to April 2011, certified the association between HRQOL and various sociodemographic factors, surprisingly, the body weight and sputum smear or culture conversion were included[62]. Due to the contagious nature of disease, TB could affect mainly the working or productive age groups (15 to 64 years), this resulted into the productivity reduction in individual, family and community which inversely did proportionate the rising level of debt and financial burden [63]. Compared to PTB counterparts, MDR-TB patients suffered more financial burden, so they worried about safety and security in living and working conditions, which in turn affected QOL[29,43] .

Rajeswari study in India[63] , mentioned that employed patients expensed of the mean indirect cost (Rs.3863/-) for diagnosis and treatment, even they lost about half of their working days (48/83 days) before treatment initiation. Most of the patients' wages and salaries were spent on indirect costs which were higher than direct costs as a result intervening the health-seeking for appropriate diagnosis and treatment. This Indian figure showed alarming trends of the increasing indirect TB expenditures especially women suffered more due to the social stigma and discriminative nature of the Indian society[63]. Again in Zambia, the patients used 60% of their mean monthly income as direct costs for diagnosis, which was nearly 5 to 10 times higher than the World bank previous recorded data[64].

In an Eastern Ethiopian study, almost all patients dropped out from work after getting the disease, so they encountered severe financial challenges,[46] likewise in a Mexican study, almost all the participants were not able to work, perhaps due to the ADRs and their perceived feelings about their jobs which really affected their income and financial situation, finally they needed financial assistance and they became dependent to others [26] .

". . . [his] salary was cut in half . . . since it [was] considered [a] risk to work with TB . . . [the] capital must approve [to work] and return your full salary. (extracted the speech of male MDR-TB patient, 47 years)"[26] .

Thus, consideration to improve the treatment adherence, the provision of free drugs alone was not a solution and there was a need to consider financial support. It could help to reduce the patients' psychological distress like stress, anxiety, worry and depression, after that, to improve the treatment adherence, all of these factors could bring a substantial improvement of QOL[65] . Either social safety and security, care and support from family and community had also a positive influence on the QOL [61]. Overall, education had a significant association on all domains through evidences, like more educated patients got four times better HRQOL scores compared to illiterate patients (OR = 4, 95% CI: 2.3, 7.3)[66] . Education was related to awareness and self-care[20] , so well-educated patients with a good health literacy managed to self-care and stress management properly and recovered quickly. Through their flexi-arrangements of employment status, financial issues, health-seeking behaviours towards the improvement of well-being and QOL in long-term aspect[44,49,67].

The majority of findings agreed that physical health was the most affected area in all QOL domains. This fact was again confirmed by the study findings from Chamla and Guo N, in addition, almost all the scores improved due to the effectiveness of anti-TB drugs in which the physical health domain was the greatest responder and it had a positive correlation with HRQOL [45,68]. Different in Muniyandi's South Indian study,[69] which was conducted in 2003 – 2004, highlighted that although with an effective anti-TB treatment, about 40% of study patients had remained persistent physical symptoms even after one year of successful treatment, and their HRQOL scores were prominently lower than the general population. TB and MDR-TB had a negative impact on the financial situation of the patients' and their families, that stated in studies of (46,63,64,66).

3.3 Treatment related ADRs or side-effects and perceived drugs side-effects

There were plenty of articles related to TB and MDR-TB treatment side-effects. The way of presenting drug side-effects of MDR-TB treatment were different studies from studies, which were probably caused because of a different context, study population, study instruments and study limitations. Among them, one retrospective cohort study was conducted from reviewing the medical records of 60 Peruvian MDR-TB patients, who were being on treatment during 1996 to 1998 by Furin, et.al[70]. The findings revealed that the majority of patients suffered ADRs such as "mild gastritis (100%), dermatological effects (43.3%), peripheral neuropathy (16.7%), depression (18.3%), and anxiety (11.7%)". But hepatitis was reported only by 1.7% of participants which was lower than the 30% in previous Peruvian studies. In that study, the most common one was peripheral neuropathy (16.7%) mainly due to streptomycin, isoniazid and ethionamide drugs from the MDR-TB treatment regimen[70] .

Similar findings were seen in another Peruvian chart review study, performed by Shin SS, et.al within 1996 – 1999, the peripheral neuropathy, commonly contributed to (13%),[71] and other less frequent side-effects were renal failure, optic neuritis, and hypothyroidism. Psychological disorder like depression was slightly common as 18.3% but ADRs was not absolute contraindication for suspension or discontinuation of the MDR-TB treatment[70]. In Tembeka's study in Johannesburg, South Africa, a total of 58 (38.9%) among 149 DR-TB patients, suffered side-effects in the intensive phase including joint pain, peripheral neuropathy, hearing deficit, nausea, vomiting, dizziness and vertigo. The overall summary scores for PCS was lower in patients with ADRs than patients without[72]. In the 12-years retrospective Turkish cohort study (1992-2004) among 263 MDR-TB cases, Torun observed different findings, that the common side-effects were "ototoxicity (41.8%), psychiatric disorders (21.3%), gastrointestinal disturbance (14.0%), arthralgia (11.4%), epileptic seizures (9.9%), hepatitis (4.5%), and dermatological effects (4.5%)". Out of 263, 182 (69.2%) developed one or more ADRs, and 145 (55.5%) needed to withdraw some drugs from their treatment[73].

Another confirmed findings that the majority of patients experienced and perceived drug side-effects during the treatment so they were not able to work well then left their jobs which all these factors drove them to poverty and a low QOL[26]. Observed in a Canadian study, Marra CA clearly stated that TB had a large negative impact on the patients' QOL, the main reason was the unwanted ADRs[55]. Eighty-nine percent of patients suffered minimal one side-effect during their treatment, they also complained about the number and timing of drugs, painful injection, the costly and lengthy treatment which forced them to stressful conditions and affected their HRQOL[47] .

In Nepalis, a qualitative study via semi-structured interviews (SSIs) and focus group discussion (FGDs) was conducted by Khanal. Almost all participants responded as MDR-TB disease and its treatment had the greatest impact on their physical health mainly due to ADRs including bodily and joint pain, and movement limitations. So, they could not perform well by themselves, even the daily routine activities.[74] Also the observed findings in a South African by Ana Maria Kelly, the six common ADRs were "tinnitus, gastrointestinal symptoms such as nausea/vomiting and diarrhoea, and movement-related symptoms like myalgia, arthralgia, and peripheral neuropathy" which associated with a low HRQOL[75]. In Eastern Taiwan, the QOL of TB patients were measured on three different occasions at treatment initiation, 2-months, and 6-months after treatment by Chung through population-based prospective cohort study during March to July 2007. The results were different from other studies, which highlighted that among the side-effects, hepatitis had a statistically significant association with low QOL scores and also the blurred vision as well[76] .

3.4 Patients' knowledge, beliefs, and perceptions about the TB and MDR-TB diseases

In terms of TB and MDR-TB patients' beliefs and perceptions about QOL, their knowledge about the illness-related symptoms, diagnosis and treatment-related factors were important to consider. Also, length of hospital stay, side-effects, social relationships, patients' adherence on treatment, and willingness to recover were important as well[61] . An Ethiopian qualitative study of Sahile, the respondents were aware that drug adherence was the main important theme for successful treatment and if not, TB could progress to MDR-TB. which was more severe and difficult to treat? The two informants recalled their memories of a desire to discontinue the treatment, due to the perceived wellness during treatment, but they continued their treatment until completion after consultation with health care providers. Because they realized that adherence to treatment until treatment completion was an important factor for successful treatment[57]. Basically, the patients' beliefs and positive perceptions about the treatment, knowledge and practices, including good adherence and proper infection control measures, were closely interrelated with treatment success and long-term QOL well-being.

As perceptions, which were different depending on gender, as shown in the study of TB patients who lived in Poland and diagnosed at August 2012 – January 2013, the popular lay beliefs among male patients was that they were more vulnerable to get coinfection than females and then, alcohol consumption and psychotropic drugs could reduce a certain amount of stress. In reality, alcoholics and drug-addicted patients had a lack of proper compliance and cooperation with health care providers. The authors mentioned as "In women, health behaviour most frequently concerned the subscale of prevention strategies, and in men, the subscale of positive mental attitude", so there was a slight difference in health behaviour and stress management style, however, there was not so much significant difference in QOL aspects between the sexes [77].

A cross-sectional study was conducted, to assess a total of 217 MDR-TB patients' knowledge and practices, in Aung San TB Specialist Hospital, Yangon from September to December 2014. There was a statistically significant association between communication with health staff and the MDR-TB patients' knowledge and practices. The counselling, health education, and proper distribution of IEC materials for Information, Education and Communication showed a marginal association with the patients' perceptions and adherence improvement to get better QOL results[78]. Further findings mentioned that almost one-third of patients was not aware of the high-risk individuals for TB. Regarding practices, although 98% responded to the correct cough etiquette, only 94% practiced it in reality and 15% used the proper sputum disposal methods. Moreover, Sahile stated in their qualitative study, the QOL correlated with patients' beliefs, perceptions and knowledge about the disease, followed by individual practices, also differed based on their knowledge, thus, a low level of knowledge and false beliefs harmed QOL[57,78].

In fact, the relationship between health care providers and MDR-TB patients had a significant correlation on the patients' practices, so the role of health care providers was one of the influencing factors on the patients' adherence, successful treatment, and improvement of their QOL. In Myanmar, the dealing between them was good in 53.5% of total respondents, 44.2% was fair and only 23% was poor and similar results were found in Ethiopia [57,78]. Amazingly, some Canadian participants had negative views on disease, diagnosis and treatment including about the health care professionals who were needed more update knowledge and skills for early diagnosis and prompt treatment[55].

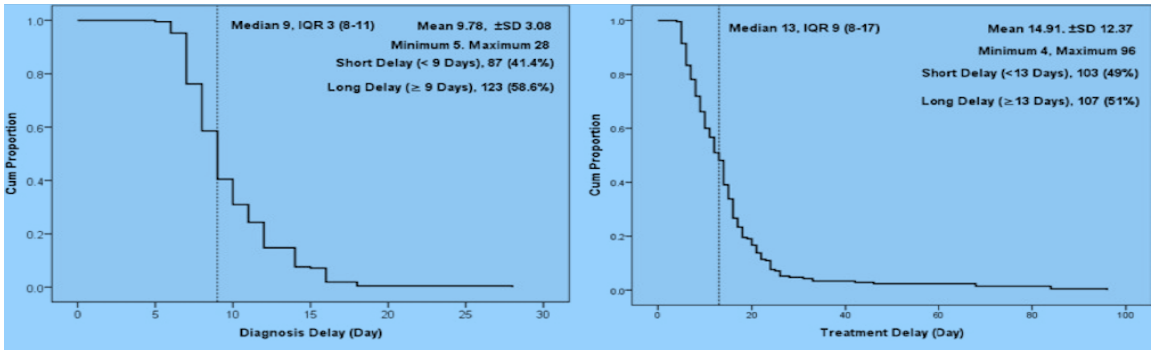
3.5 Accessibility to MDR-TB related health care services

In an Ethiopian study, Sahile stated that almost all participants responded, that designated health care facilities were located near to their households, except two informants, they resided slightly far away from facilities, so they costed the transportation fees to reach

there. Despite that, there were no difficulties for follow-up visits, even in their daily intensive DOTS period. Generally, the patients complained about the waiting time for health care professionals, which was the maximum in the intensive phase, after that getting lesser and lesser. The difficulties in accessing health care services were barriers for successful treatment and had indirectly impact on QOL improvement[57]. Many studies highlighted the point of disease and treatment related direct and indirect costs imposed the financial burden to patients (45,57,63,64,66).

Similarly, in Myanmar, about 58.6% of study participants experienced the median diagnosis delay as 9 days, and 51% faced the median treatment initiation delay as 13 days, which were longer than the findings in neighbouring high TB/ MDR-TB burden country, Bangladesh[20]. In which it was stated as "the median of diagnostic delay (5 days), treatment initiation delay (10 days) and provider delay (4 weeks) from the health system side"[25]. There were many reasons for diagnosis and treatment delay, not only the ineffective health care system but also patients' factors including patients' negative perceptions, lack of knowledge, improper health-seeking behaviours and delay in accessibility of the health care services. Unemployment, comorbid conditions had also a significant association with longer delaying time [20]. So, diagnosis and treatment delay influenced the treatment success and related to QOL scores.

Graph – 4: Delay in Diagnosis and Treatment Initiation among 217 MDR-TB patients in Aung San TB Specialist Hospital, Yangon, Myanmar [20]



According to the WHO definition, "health is defined as a state of complete physical, mental, and social well-being and not a mere absence of disease or infirmity". So, patients well-being could not defined only based on the clinical or laboratory clear results because the disease was markedly affected to QOL in long-term and the residual impairment were also frequent[79]. The Kittikraisak's study of health utilities, among 222 TB patients in Thailand, mentioned that a comprehensive holistic health care approach could improve the patients' QOL and encourage them to keep their strength up in daily lives [80]. The study on the effects of DOTS on daily living activities and QOL of TB patients in another SEAR country, Singapore was conducted by Lee in May 2013 – April 2014. Although, most of the patients aware that DOTS was important and effective in TB treatment, almost two-third of the study participants complained about that DOTS interfered with their daily activities[81]. Because of the waiting time and the transportation costs increased to go to the health centre daily. So, the community trained volunteers role was important in DOTS activity at the community level and then, collaboration between healthcare workers and the community in an assisting role to the patients, beyond the treatment period, was also important [81].

3.6 Effects of stigma and discrimination on the patients' sexual and personal relationships concerning QOL

According to Laxmeshwar's study results[42], the participants had well-known social effects due to the disease and its treatment. As a result, they were not able to participate in social activities and social functioning. In some societies, the social stigma on TB was prominent,

therefore TB patients endured the prejudice, health stigmatization, discrimination and social isolation from their loved ones that fuelled "social death and health stigmatization". "*Health stigmatization* may be defined as a social process characterized by exclusion, rejection, and guilt, or the devaluation resulting from the experience of unfavourable social judgment due to a particular health condition" [82]. They encountered stress, anxiety, feelings of guilt, fear of disclosure, fear of transmission to their loved ones and fear of death, which aggravated negative reactions like isolation and loneliness, it resulted into the worst QOL[31,53].

Another relevant study of Morris[26] certified that the patients' perceived social isolation was derived from the discrimination of their families and friends, then self-isolation and self-stigma to protect their loved ones from disease transmission. The patients' main concern was the negative responses from others, so they cut all kinds of communications after getting a diagnosis[26]. Their perceived risks of infection made them quit from jobs and communities, consequently, causing a loss of income, lack of social activities and separation from community networks appeared. One participant reported that;

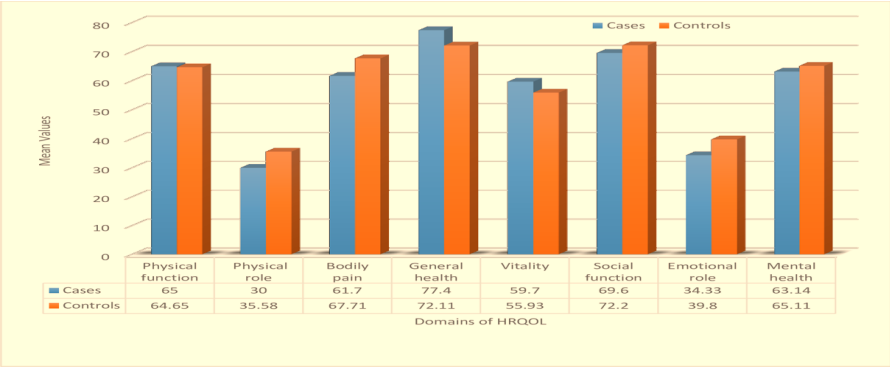
"They would ask me to leave . . . because they didn't know that it is not contagious in the open air

. . . And they said, 'then leave us with our ignorance and go home, don't come here anymore.'

And if the children were there and I arrived, suddenly there was nobody. (extracted from speech of male MDR-TB patient, 45 years)"[26].

Moreover, the majority of patients encountered the consequences of disclosure even from the health care professionals, so they went away from this ill-treating environment. The financial issues added also a great deal to the patients' stress, mental health problems and impacts on QOL[67] . Another Thailand's study, for the perspectives of TB stigma in PTB patients, who enrolled in (Aug 2005 – July 2006), even one unit of TB stigma increased to a longer delay time for health care seeking in men (0.012 log-delay) whereas, the opposite results were found in women, who were exposed to a higher TB stigma they might be seeking the health services promptly for relieving their sufferings. Actually, stigma could influence health care seeking behaviours which was directly associated with QOL[83] . The Indian observational study of Sonia, et.al reported that the majority of participants suffered the disease-related negative impacts on their social and sexual relationship, because they lost their sexual interests due to generalized weakness, all these factors brought the lack of a sense of worth and a meaningful life[84]. Certified results from an Eastern Ethiopian study, MDR-TB patients suffered more unlimited stigma and discrimination from communities, compared to non-MDRTB patients,[46] so stigma had an influence on social well-being[69]. Depending on the age and gender, the overall mean scores of QOL were differed due to the uneven exposures of stigma and discrimination found in the studies of (48,49,67).

Graph – 5: Mean differences of HRQOL domains between MDR-TB cases and TB control groups in Eastern Ethiopia from February to July 2017 [46]



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3.7 Role of Social Support and Community Networks in MDR-TB patients

In PMDT activities, the role of effective counselling, better health education to patients, household contacts and the communities were important in supporting, preventing unnecessary stigmatization and isolation [85]. In Khanal's qualitative study[74], the MDR-TB patients highlighted their sufferings of psychological distress which could distance them from social networking and impact on their relationships. To overcome these challenges, they acknowledged the value of family and psychosocial support from communities.

Generally, TB was a well-known risk factor for the impaired mental well-being of patients, apart from who received well-support of families and societies, they could overcome these problems, and this resulted into good HRQOL outcomes. This statement was complimented by a Zimbabwean study in TB patients, who received great social support that optimized their HRQOL score, than patients without social support (68.8% variance)[86]. The comparable results were found in a Myanmar study, the old-aged people who depended on others, who could not manage by themselves, without family support. Therefore, the role of social support, through community participation together with the health care workers efforts, were essential for patients' motivation during treatment[20].

The first global study conducted to assess the effect of domiciliary care to MDR-TB patients, enrolled from January 2015 to June 2016, through community-based programs in Myanmar, which was effective and supportive to treatment initiation and prevent disease transmission. Key implementers were community trained volunteers, so again highlighting how important the community involvement and community networks in TB management sector are [87] . More study from the Puducherry's community DOTS centre, through SF-36 amongst 92 TB patients and 83 controls, certified the evidence of DOTS which offered a great improvement in treatment success and long-term QOL in cases than controls who ensured great support from their family and communities[88].

In July 2000, the study findings from 51 culture-positive TB patients in Yangon, the drug-resistant rate was as high as 33.3% in at least one of the first-line anti-TB drugs, which indicated that the drug-resistant problems still pose a threat to TB control activities in Yangon. The possible reasons were coinfection, drug side-effects and fear of disclosure to the previous anti-TB treatment history, which lessened drug-adherence and increased drug-resistance. Therefore, the NTP and MoHS need to mitigated this problem urgently with integration of a holistic approach, DOTS and community-based care with social protection measures[89]. The role of psychosocial support from family and society were important in TB control activities, also the community participation and collaboration of healthcare workers were essential, which mentioned in majority of the studies (20,74,85,86,88).

3.8 Impacts of MDR-TB on mental health and spirituality

In the Apoorava's study, the common psychological symptoms were negative feelings and perceptions about the disease, hopelessness, poor self-confidence and loss of identity[68]. Simply, a qualitative study in DOTS plus program of Tamilnadu, presented the most psychological issues were fear like the fear of disclosure, fear of death, fear of survival along with guilty or self-blaming, psychological trauma and depression [67].

Morris's study certified again the fact that fear and hopelessness were common after getting the disease, one patient stated,[26]

"I felt very upset because I was already overwhelmed [when diagnosed with TB], then I was diagnosed with MDR-TB, and was told there is no medicine in Mexico for [me], they told me this may be treated but it is very expensive and only available in the United States. (male MDR-TB patient, 60 years)"[26].

Another Peruvian retrospective case-series (1996 – 1999) was presented by Vega as the baseline data for depression, anxiety, and psychosis, 52.2 %, 8.7% and 0% respectively. The incidence rates during the treatment were 13.3%, 12.0%, and 12.0%, which were relatively higher than the general population prevalence, but psychiatric problems were not contradicting the MDR-TB treatment continuation. The increasing impacts of depression, anxiety and psychosis, during treatment, seemed to be related to drugs side- effects [90]. The ones with depression had five times poor social relationships (OR = 5.3, 95% CI: 2.3, 14.2) and an 8.8 times higher chance of impaired physical health than non-depressed people (OR = 8.8, 95% CI: 3.2, 23). Again, stigma and spirituality were negatively associated with poor QOL[63].

It was observed in a Turkish retrospective cohort study, that 21.3% of patients experienced mild to severe psychiatric disorders, like depression, anxiety, psychosis, even suicidal thoughts[73]. But, Peruvian findings contradicted the former statement, because the data showed a decreasing trend of about 12-13% from the baseline after being on treatment with anti-psychiatric drugs and psychosocial support[70]. In Penang General hospital's findings, the depressive disorder was common in almost 70% of studied patients (MCS score ≤ 42 Norm-Based Scoring; NBS point) at their treatment initiation [31]. Indeed, most respondents reported that guilty feeling, fear of dying and hopelessness after getting their diagnosis[66,82,85] . They were worried about the affordability, drugs availability and their QOL in the future although they were on treatment. Though anti-TB treatment relieved the substantial psychological symptoms, approximately 23.5% of patients still had a risk of depression after treatment completion[33]. Not surprisingly, those patients felt themselves as a non-valuable person and had a lack of a sense of identity, which further turned into self-isolation, and more psychological problems.

Deribew, et al. studied in Ethiopian TB/HIV coinfected patients, the poor QOL scores strongly corrected with depression and stigma ($P<0.05$)[66]. Lower MCS scores meant that the patients suffered RE limitations due to psychological distress and emotional stress [31]. In contrary, being married and family support, created a strong protective effect on psychological problems[53], so psychosocial support was a prioritized intervention in TB management activities[55]. Another of Deribew's work in Ethiopia, described as Common Mental Disorder (CMD), was a common psychiatric disease, it had a strong association with QOL ($P<0.001$)[91]. Yet, both Ethiopians works confirmed that mental distress and CMD were the major influencers on QOL [85]and again, the TB/HIV coinfected patients, who suffered a high social stigma, led to CMD as well[53].

Regarding prospective follow-up study of the patients who took the treatment during (October 2012- September 2013) via SF – 36v2 at lady Reading Hospital Peshawar, the average MCS scores, measured at three occasions, were (33.7±7.0, 35.5±6.9, 40.0±6.9) respectively which depended on gender and illness duration before treatment [92]. In the

Dhuria"s Delhi study, the psychological aspect stood at the second most affected domain (9.82 ± 1.98) and the mean QOL scores in men were better than women, but there was no significant difference between the sexes [50]. Adeyeye's Lagos study differently reported that the psychological domain score was (66.75±16.60) in which female scores were superior to male[49]. However, Laxmeshwar stated different results from Dhuria and Adeyeye, the psychological was the most affected (56.2, SD 15), and the male score were lower than female due to stress, anxiety, and depression [42].

In Yemenis' prospective HRQOL study in TB patients who are taking the treatment between March 2013 and February 2014, it revealed that the mean MCS scores resulted as 35.1, 42.2 and 44.3 found at treatment initiation, after intensive and treatment completion period. Although, the treatment brought increased QOL scoring, which was still below the NBS and the patients still had a chance of psychological risks [93].

Table – 13: Changes in Physical and Mental Component Summary (PCS and MCS) during various stages of treatment, Yemen[93]

Component Summary	Mean score (SD)			Alteration of Mean score
	Start of Intensive Phase (N=243)	End of Intensive Phase (N=235)	End of Continuation Phase (N=197)	
PCS	36.1 (6.6)	44.9 (6.6)	48.9 (7.8)	12.8
MCS	35.1 (11.3)	42.2 (11.7)	44.3 (13.1)	9.2

Kastein-Hilka's results confirmed that overall sores in all domains were statistically significant improved throughout the treatment and the most prominent one was the mental health domain [52]. Recognizable psychological distress in TB patients depended on the different contexts, cultures, and understandings. Therefore the reduction of the TB burden had an association with improvement of community health literacy and the interventions, such as effective counselling and psychological support strategies [94]. Many findings certified that TB and MDR-TB patients suffered various forms of psychological problems during their treatment, some of them had persistent symptoms beyond treatment completion, which severely affected to QOL in long term (33,63,66,73,90).

3.9 Discussion

In summary, nowadays, the increasing burden of TB and MDR-TB led to threat the global TB prevention and control activities. Currently, similar conditions happened in Myanmar which serves as a barrier to the country's commitment of END-TB strategy and UHC pathway. With updated treatment guidelines and effective health care strategies, it can be said that certain levels of TB related mortality can likely be reduced, so serious attention to TB management activities, from numerous global TB programs, has shifted to a patient's charter care, to improve the well-being of beneficiaries, including all QOL aspects. Although, the assessment of HRQOL, delivers a certain value to evaluate the NTP performance, the current testimonials, in particular neglected areas, are QOL aspects such as physical, psychological, social and environment associated with MDR-TB disease, its treatment, and impacts through short-term and long-term . Therefore, this study was designed to highlight the most likely leading factors to MDR-TB and its determinants on HRQOL among MDR-TB patients and to explore its applicability to a study context: Yangon, Myanmar based on the developed conceptual framework of four domains of QOL.

The main observed findings from the literature review were some discrepancies between the various studies, because of the differences in sociodemographic and cultural factors, study sample and population, study types and methods used and eventually, analysis and the study limitations. Overall, the observed salient findings were, the physical domain was the most affected area with the lowest QOL scores, amongst all domains followed by

psychological, social and environmental. Physical functioning was the most affected area due to bodily pain and limitation of movement. Though the worst scores were found in physical health, it had a great response to anti-TB treatment and its scoring was rapidly progressed during the treatment.

In relation to four domains of QOL scores, Davishpoor[33]revealed that the physical health domain was the lowest of QOL scores among four domains, in his Tehran study. This finding was similar to other studies such as Chamla [45] and Deribew [85]. In the physical health domain, RL was the worst affected and GH was the least affected area which was confirmed again by another Deribew's study[91]. However, different findings found in Sharma's Indian study,[29]the psychological and environment domain scores suffered more than physical and social domain, among them the environment showed the worst QOL scores because of the negative feelings and limitation on movements.

Also, in terms of the MDR-TB disease and its treatment, the overall scores of MDR-TB patients were poorer compared to PTB patients, especially when they spent their money for the direct and indirect costs of diagnosis and treatment of disease [29]. The majority of patients left their jobs due to treatment and side-effects, which were imposed by social stigma and discrimination,[29]similar to the findings of Rajeswari R, et.al [63]. In addition, Sharma stated that the social role, psychological distress and health perceptions, were affected, due to disease, which findings had coherence with the results from Chamla[45]. The findings from the Chamla study in Wuchan, China[45] also agreed with the Davishpoor[33] findings that of the most affected QOL areas was the physical health domain but against Sharma[29] , with results of lowest score in environmental domain. A study carried out by Louw J[41]in South Africa, showed that the most affected scores were found in emotion, GH and BP while the highest scores were found in energy, fatigue and MH in TB/HIV coinfected patients. This finding was in contrast with Deribew,[66]who mentioned that all domains scores were lower in coinfected patients than in the control groups. In addition, the Babikko,[30] and Chamla [45] findings disagreed with the point of age and sex had no significant association with QOL as mentioned in Louw J[41] study.

Another Indian study performed by Apoorva E[43]showed evidence to confirm the physical and environment scores, were statistically significant lower in MDR-TB patients compared to non-MDRTB patients, and their physical and psychological scores were also lower than cured DSTB patients. So, the physical health was the common most affected area and these findings were similar to Sharma [29], Aggarwal[51] and Chamla[45]. Additionally, the Philippine study[44] for MDR-TB patients confirmed that the physical health domain in both TB and MDR-TB patients, was the most affected area and sociodemographic factors such as age, gender and SES had an association with QOL scores. Study conducted by Mamani in Hamadan,[40]stated that TB had a severe negative impact on QOL of infected patients, which had comparable results from Duyan's study[61]. The overall score of PTB patients was remarkably lower than the general population at baseline, however, its improvement could be seen throughout the treatment period[40].

Even though the greatest improvement was found in physical health, some patients experienced the residual symptoms after a successful completed treatment[40], which is also certified by findings from Chamla[45] and Guo N, et.al[68]. The latter agreed with the Thailand study,[80] which showed that the health utilities of TB patients were improved during the treatment period, this meant that the improvement in health conditions due to effective drugs, especially in physical health, so the patients had motivation and willingness and effort to recover from the disease.

In Dhuria's findings,[50]the similar results showed that the most affected area was in the physical domain, but different findings in female scores, of physical and environment domains, were better than males, but female suffered more in the social domain. A Nigerian study by Adeyeye,[49] stated also that the female scores in the psychological and social domain were better than male which was versus the study of Muniyandi[69]in which females

got lower scores in those domains, due to socio-cultural differences. Rajkumar[48] described that MDR-TB had a negative impact on personal relationships, sexual activity and social participation of patients, similarly, Chamla[45]also mentioned this point in their study.

TB and MDR-TB are socio-economic related diseases and they mainly affect the vulnerable, poor population. Deribew[66] and Duyan[61]highlighted that the well-educated young male patients, with a high SES, living in urban areas, had less disease-related symptoms and better QOL scores than their female counterparts. Regarding ADRs, Laxmeshwar[42] described that the psychological domain was the most affected, due to drug side-effects in the DR-TB study population, but the score was not so far less as the findings of Guo N,[68] Brown J[39] and Aggarwal AN.[51]Apart from side-effects, the common predictors for low QOL in that study were depression, fear, stigma and health-system related factors. Another important points were the reactions from health care providers, family and workplace that had prominent effects on the patients' QOL, so the social and psychological support from them was essential to improve the patients' QOL scores[42].

The majority of patients, experienced treatment-related side-effects, this resulted into impacts on compliance and adherence of patients, which was the main predictor of successful treatment, and long-term well-being of QOL. Another negative impact of the disease was the burden on socioeconomic situations, which put on a weight of catastrophic costs, due to the loss of jobs and income, productivity reduction pulled them into debt and into a poverty cycle. Other proxy predictors of MDR-TB were individual general characteristics (age, sex, education, lack of knowledge, smoking and alcohol abuse), comorbid conditions (DM, HIV) and health-system related factors, which had an influence on QOC. Compared to the general population, the overall QOL scores of infected patients were significantly harmed by a long-term impact even after treatment completion, mainly in mental well-being, because of emotional distress, distress, trauma and psychological problems related to the disease.

The common complaint about psychological distress were fear, such as fear of disclosure, fear of transmission and fear of death, feelings of guilt, anxiety, depression and worries about future prospects which stressed the patients' emotion and led to self-isolation and separation from their families, social and community participation. Depression was slightly common derived from the disease and its treatment side-effects, also imposed by stigma and discrimination from family, friends, and communities, consequently, severe impacts on the patients' psychology, social and personal relationships. Surprisingly, findings from a Namibian study[47]showed that ADRs had no significant influence on QOL domains.

According to findings, it can be concluded that the vicious poverty cycle occurred between MDR-TB and QOL, because MDR-TB affected the poor population and those people suffered disease and treatment consequences, which created a low QOL and a lack of worth sense. Therefore, the TB and MDR-TB treatment needed more attention with a comprehensive care approach, not only with the clinical aspects, but also QOL aspects and the well-being of patients. There are many success stories about the patient-centred approach and a community-based TB/MDRTB care activities in Myanmar and globally as well.

This study has some limitations, since a few studies and papers are published and there is limited access to online libraries for the QOL of MDR-TB patients in a similar study area. The most important limitations are probably that there is still very limited research done particular in studies on QOL in TB/MDR-TB in resource poor settings. Given that most is from other countries than Myanmar, care has to be taken when trying to extrapolate these findings to Yangon.

4. Conclusions and Recommendations

4.1 Conclusions

Although there are limited evidence-based studies related to QOL of MDR-TB patients, it is clearly realized that the disease itself and its treatment have negative impacts on all domains of QOL. Therefore, the current study highlights that PMDT activities should be enhanced by integrated patient-centred CBTBC and support activities. Hence, a rapid diagnostic tests and anti-TB drugs are effective against the disease, providing a package of support, including psychological, financial , nutritional, social support and social protection measures are also essential for long-term improvement of QOL and well-being of beneficiaries. In addition, the profound long-term impact on the psychological domain called upon serious attention of health care personnel, so supportive counselling, stress management and effective health communication are urgently needed. The reduction in patients' psychiatric problems, social stigma and discrimination, inequalities in accessibility to health care services and poverty reduction strategies are needed to proper address it. The QOC that the TB/MDR-TB patients received is also an important proxy predictor of QOL, thus, provision of early diagnosis, prompt and effective treatment, adequate management of side-effects from health care providers is important. The improvement in health literacy, compliance and adherence to treatment and the proper following of the treatment-related instructions are important responsibilities of patients, to prevent further transmission and to promote a quick recovery with a meaningful life. Community participation in TB/MDR-TB control activities is also essential to reduce social stigma and discrimination. Briefly, the collaboration and uniting of all the stakeholders, such as health care providers, patients and family members and lastly, the community is important to end the TB/MDR-TB diseases.

4.2 Recommendations

4.2.1 General Recommendations

4.2.1.1 In the current study, the main findings from specific studies are outside the study area of Myanmar, therefore NTP and MoHS are needed to conduct additional work, to undertake operational research studies focussing on TB/MDRTB and its impact on HRQOL according to fulfil the Strategic Direction III of the NSP (2016-2020) (Annex – 4).

4.2.1.2 It is still difficult to browse and search for abstracts and full-text articles, related to HRQOL in Myanmar through search engines, databases, and the online Burma library. Therefore, the government should promote the broad accessibility by local and international researchers and their collaborations in research works, in this limited low source settings.

4.2.2 Specific Recommendations to NTP and MoHS

4.2.2.1 To provide the QOC to TB/MDR-TB beneficiaries, the NTP should accelerate and expand the existing PMDT activities, as effectively and efficiently in case-finding and case-holding activities, early diagnosis and prompt treatment, proper management to ADRs and to strengthen the health-system.

4.2.2.2 The Government should create effective management strategies to improve the accessibility of health care services, inequality reduction, especially in socio-economic conditions, financial matters as disease-related indirect or catastrophic costs.

4.2.2.3 The MoHS and NTP should ensure that all MDR-TB patients can in equitable access to treatment enrolment and have availability of the package of support, including health education, effective counselling, psychosocial, nutritional and financial support through integrated approach of CBTBC.

4.2.2.4 Community awareness and health literacy are important in TB/MDR-TB prevention and control activities. So, effective health education campaigns for awareness-raising in targeting communities such as patients, family members and the high-risk population are needed. It can provide a guidance how to practice the healthy lifestyles, proper knowledge about the disease, diagnosis, treatment and side-effects, health-seeking behaviours and infection control measures.

4.2.2.5 Also, the community network and participation are powerful themes in PMDT activities, thus strengthening the capacity of the community through capacity building training and encouraging the community to participate in PMDT activities, such as health education, psychosocial support and DOTS activities, which will lead to the reduction of social stigma and discrimination.

4.2.2.6 By empowering the community networks, such as peer groups, self-help groups and community-based organizations to support the patient being ready to participate in social and leisure activities to give a sense of identity during and after the treatment. Social security and protection schemes are also needed to be implemented.

4.2.2.7 Providing continuous capacity building to health care professionals, to strengthen the knowledge and skills in early diagnosis and effective and treatment are also integral part of the TB/MDR-TB care and management activities.

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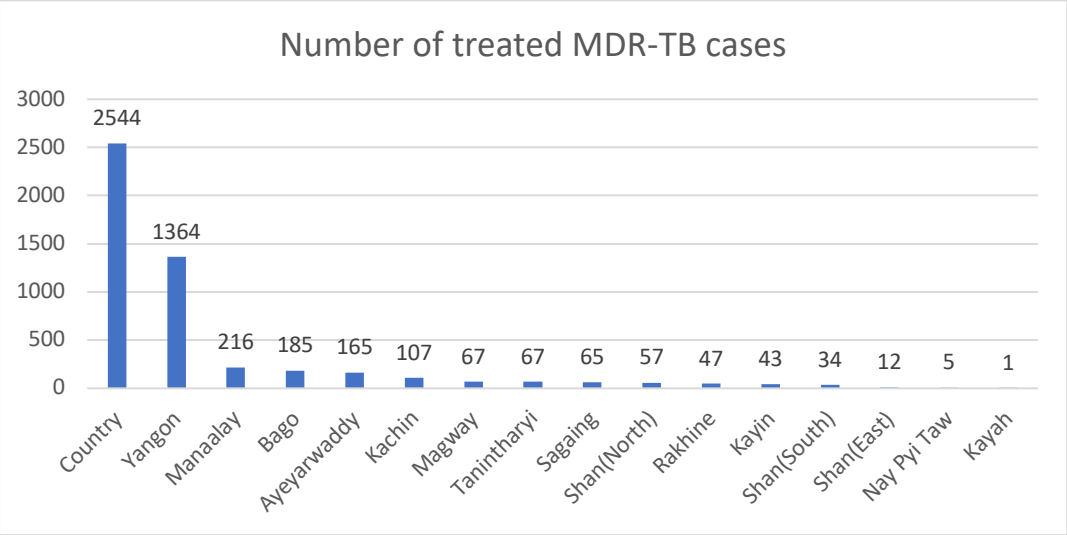
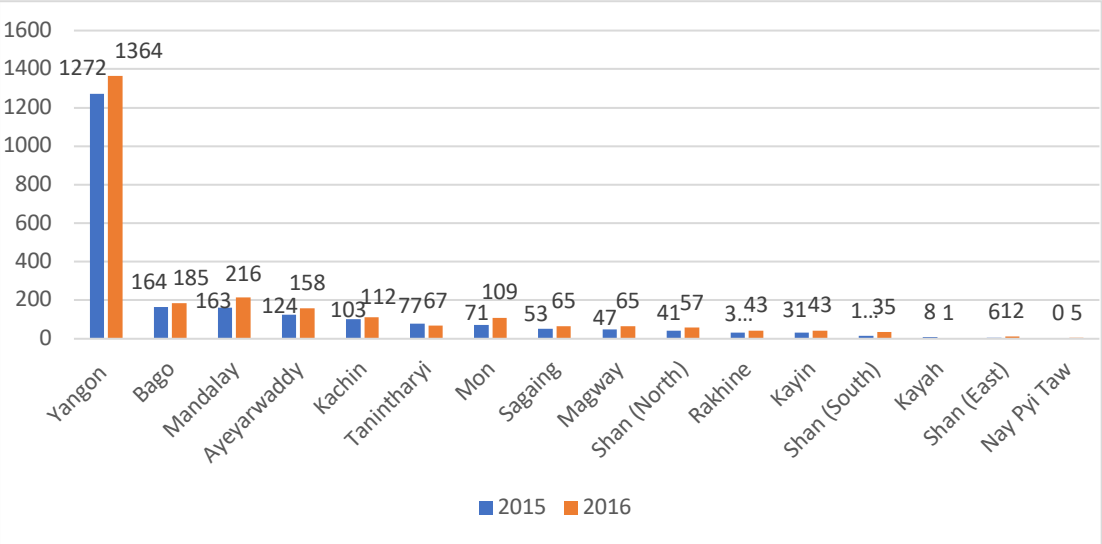
Annexes

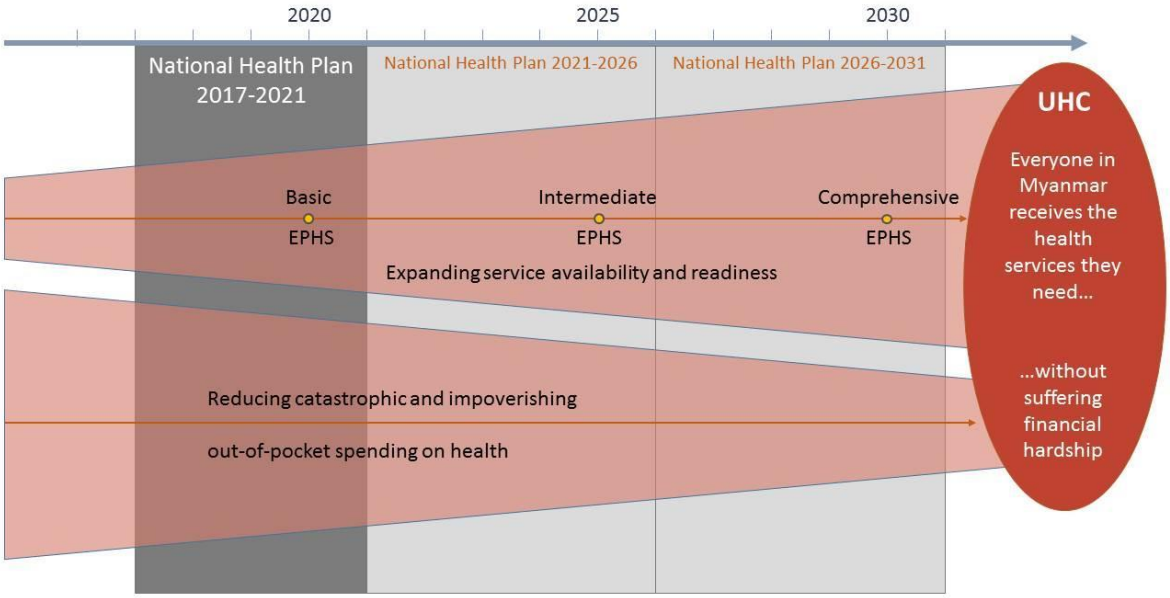
Annex – 1: Number of MDR-TB cases treated by Regions/States, Myanmar in 2016[18]



Annex – 2: Comparison of Region-wise MDR-TB enrolment between 2015 and 2016, in Myanmar[18]



Annex – 3: National Health Plan, Myanmar (NHP 2017-2021)[3]



Annex – 4: Strategic directions and key interventions of National Strategic Plan, Myanmar (2016-2020)[34]

Strategic Direction I: Integrated, Patient-centred Care and Prevention
1.1. Accelerate the appropriate diagnosis of TB
1.2. Identify and treat all forms of TB, among all ages and including drug-resistant and drug-sensitive
1.3. Prevent transmission and the emergence of active TB
1.4. Intensify targeted action(s) to reach marginalized and at-risk populations
1.5. Implement a robust communication strategy, extending from policy makers to patient education
1.6. Engage all care providers, including NGOs and the private sector, in appropriate TB diagnosis and care
1.7. Promote and strengthen community engagement
1.8. Joint TB and HIV programming to enable decentralized and integrated services for TB and HIV

Strategic Direction II: Bold Policies and Supportive Systems
2.1. Secure human and financial resources for implementation of the NSP
2.2. Promote a coordinated and multi-sectoral response and policy development
2.3. Ensure inclusion of TB in UHC and wider economic development plans and activities (social protection)
2.4. Ensure a stable and quality-assured supply of drugs, diagnostic tests and commodities
2.5. Human resources for health
Strategic Direction III: Intensified Research and Innovation
3.1. Implement the prioritized research agenda
3.2. Enhance evidence-based programme monitoring and implementation

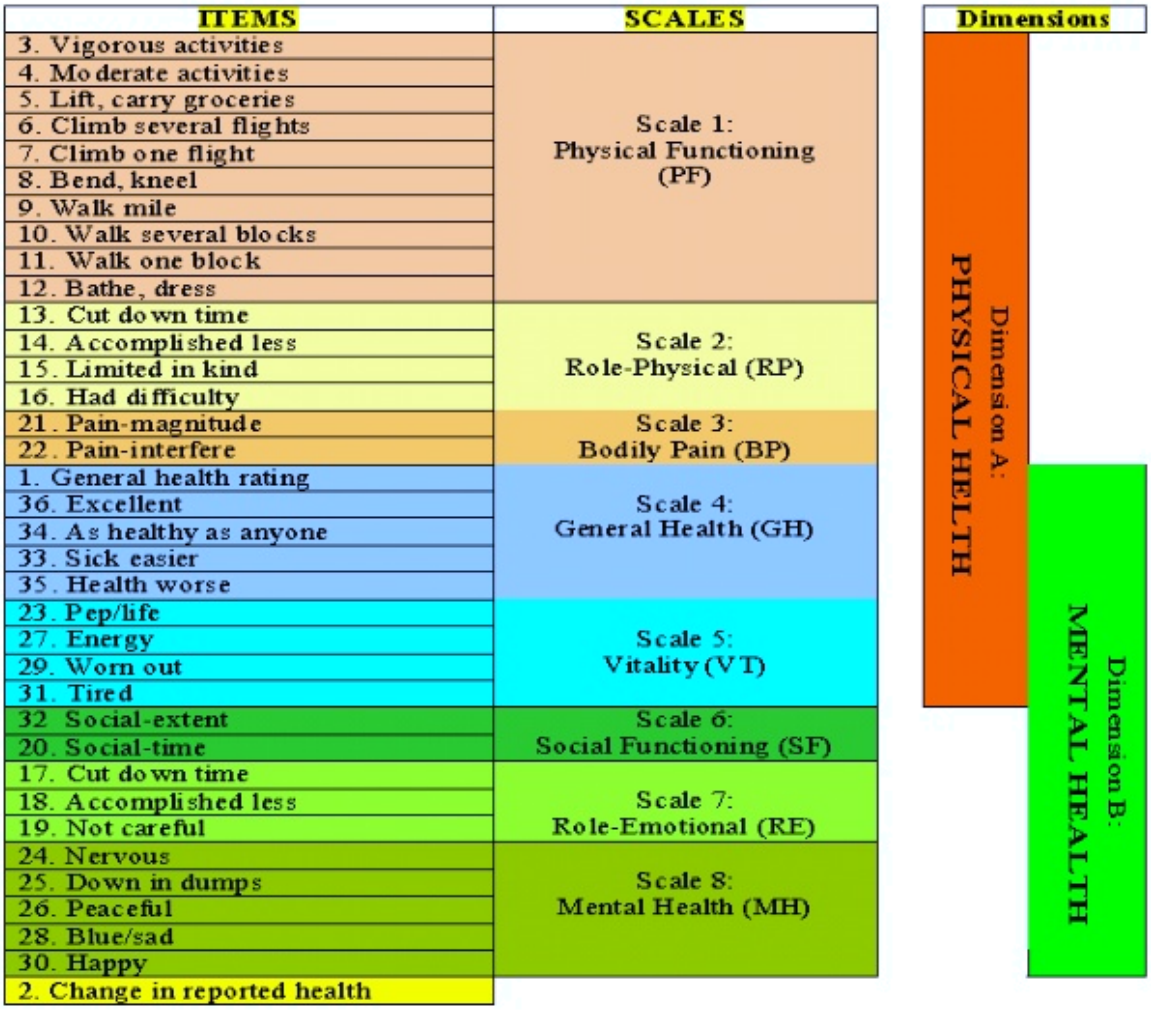
Annex – 5: Field Trial Version: WHOQOL-BREF framework for Generic Version of assessment[37]

WHOQOL-BREF domains	Facets incorporated within domains
Physical health	Activities of daily working Dependence on medical substances and medical aids Energy and fatigue Mobility Pain and discomfort Sleep and rest Work capacity
Psychological	Bodily image and appearance Negative feelings Positive feelings Self-esteem Spirituality/Religion/Personal beliefs Thinking, learning, memory, and concentration
Social relationships	Personal relationships Social support Sexual activity
Environment	Financial resources Freedom, physical safety and security Health and social care: accessibility Home environment Opportunities for acquiring new information and skills Participation in and opportunities For recreation/leisure activities Physical environment (pollution/noise/traffic/climate) Transport

Annex – 6, The World Health Organization. Quality of Life (QOL) instruments (the WHOQOL-100 and the WHOQOL-BREF Introduction)[27]

Domain	Facets incorporated within domains
	Overall Quality of Life and General Health
Physical Health	Energy and fatigue Pain and discomfort Sleep and rest
Psychological	Bodily image and appearance Negative feelings Positive feelings Self-esteem Thinking, learning, memory and concentration
Level of Independence	Mobility Activities of daily living Dependence on medicinal substances and medical aids Work Capacity
Social Relationships	Personal relationships Social support Sexual activity
Environment	Financial resources Freedom, physical safety and security Health and social care: accessibility and quality Home environment Opportunities for acquiring new information and skills Participation in and opportunities for recreation/ leisure Physical environment (pollution/noise/ traffic/climate) Transport
Religion /Spirituality/Personal beliefs	Religion /Spirituality/Personal beliefs

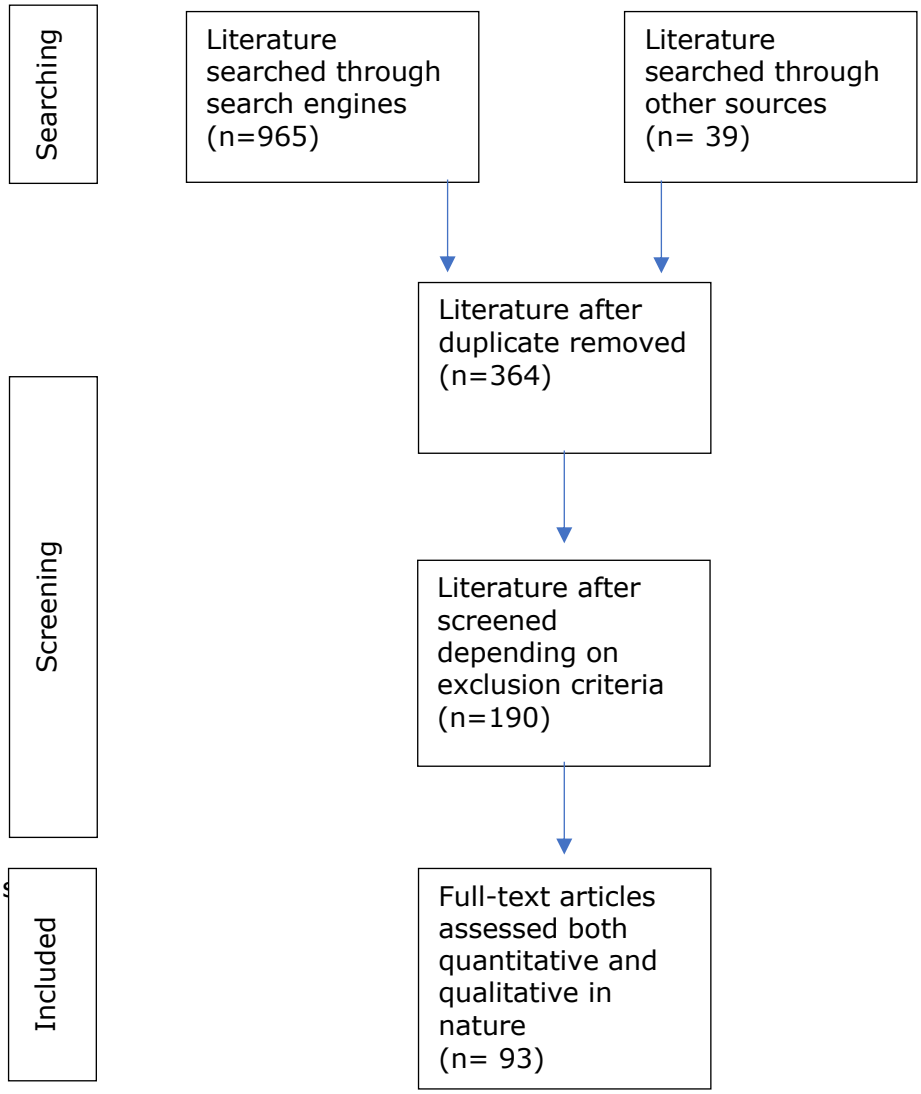
Annex – 7: The SF-36 quality of life (QOL) scoring system and its scales and dimensions. Note that *Vitality and General Health* scales are overlapping components of both *Physical Health* and *Mental Health* dimensions [38]



Annex – 8: Search Strategy

("Tuberculosis"[Mesh] OR Tuberculosis[Title/Abstract] OR TB[Title/Abstract]) OR "Multidrug Resistant Tuberculosis"[Mesh] OR Multidrug Resistant Tuberculosis[Title/Abstract] or MDRTB[Title/Abstract]) AND ("Quality of Life (QOL)"[Mesh] OR QOL*{Text Word] OR *QOL[Title/Abstract] OR "health-related Quality of Life (HRQOL)"[Mesh] OR HRQOL*[Title/Abstract] OR HRQOL[Text Word] OR Impacts[Text Word] OR Effects[Title/Abstract]) OR (Physical*[Title/Abstract] OR Psychological*[title/Abstract] OR "Stigma, Discrimination"[Mesh] OR perceived stigma[Title/Abstract] OR perceived perceptions[Mesh] OR perceived perceptions[Title/Abstract] OR Social*[Title/Abstract] OR Social Support*[Title/Abstract] OR Community Networks[Title/Abstract] OR Environmental impacts [Title/Abstract] OR "Disease-related symptoms"[Mesh] OR disease-related symptoms*[Title/Abstract] OR Illness-related factors[Title/Abstract] OR "Drug side-effects"[Mesh] OR adverse drug reactions[Title/Abstract] OR "Diagnosis, Treatment"[Title/Abstract] OR Adherence*[Mesh] OR Drug adherence[Title/Abstract] OR socio-economic[Title/Abstract] OR financial[Title/Abstract] OR Poverty[Title/Abstract] OR Education[Title/Abstract] OR Smoking[Title/Abstract] OR HIV*[Mesh] OR HIV*[Title/Abstract])

Annex – 9: Search Algorithm



Annex – 10: Instruments used to assess quality of life (QOL) of TB[39]

Name of instrument	Comments
General quality of life instruments	
Brief Disability Questionnaire (BDQ)	11-item scale; higher scores indicate worse HRQOL
Duke Health Profile (DUKE)	63 items evaluating symptoms and physical, social, and emotional function; higher scores indicate better HRQOL
Dysfunctional Analysis Questionnaire (DAQ)	50 items evaluating social, vocational, personal, familial, and cognitive domains; higher scores indicate worse HRQOL

Euro-QoL (EQ 5D)	5 domains each ranked with a 3-point scale; higher scores indicate better HRQOL
General Health Questionnaire 12 (GHQ 12)	Modified version of the General Health Questionnaire 60. Each item ranked with a 4-point Likert scale; higher scores indicate worse HRQOL
Health Utilities Index 2 (HUI 2)	7 items, each with 3 to 5 levels, used to calculate overall health utility function from 0 (death) to 1 (perfect health)
Health Utilities Index 3 (HUI 3)	8 items, each with 5 to 6 levels, used to calculate overall health utility function from 0 (death) to 1 (perfect health)
Life Satisfaction Index Z	13 items, total scores range from 0 to 26, with higher scores indicating better HRQOL
Present State Examination (PSE)	Combined general health questionnaire and self-rating depression scale; higher scores indicate worse HRQOL
SF-36 Health Survey (SF-36)	36 items covering physical and mental wellbeing. Scores from 0–100, with higher scores indicating greater HRQOL
SF-12 Health Survey	Abbreviated form of the SF-36
SF-6D utility score	11-item measure of health status. Scores range from 0 to 1.0, with higher scores indicating better HRQOL
Sheehan Disability Scale (SDS)	20 items evaluating work, family, and social lives. Scores from 0 to 30; higher scores indicate worse HRQOL
Sickness Impact Profile (SIP)	136 items evaluating personal and social impact of illness; a score of >10 indicates severe dysfunction
Severe Respiratory Insufficiency Questionnaire (SRI)	49 items ranked with a 5-point Likert scale evaluating respiratory complaints and associated physical and social limitations; higher scores indicate better HRQOL
Standard Gamble	Subjects chose between a given health state and an imaginary gamble between possible outcomes of perfect health and death; results are used to calculate a HRQOL score ranging from 0 to 1, with higher scores indicating better HRQOL
Symptoms Check List (SCL-90)	90 items in 9 domains used to calculate three global indices of global severity index, positive symptom total, and positive symptom distress index; higher scores indicate worse HRQOL
Visual Analogue Scale (VAS)	Subjects mark on a scale where they rate their own health, either using a 10-cm scale (0 cm = death, 10 cm = perfect health) or a 100-cm 'feeling thermometer'
World Health Organization's Quality of Life–BREF (WHOQOL-BREF)	26 items comprising 5 domains (physical health, psychological health, social relationships, environment) ranked on a 5-point Likert scale; higher scores indicate better HRQOL
Instruments assessing psychological morbidity	
Beck Depression Inventory (BDI)	21-item questionnaire designed to evaluate depression; higher scores indicate more severe depression, with a cut-off of ≥13 used to indicate depression
Beck Depression Inventory (BDI Short Form)	13-item questionnaire evaluating the presence of depression; overall score 0–3 = none or minimal depression, 4– 7 = mild depression, 8–15 = moderate depression, ≥16 = severe depression

Hospital Anxiety and Depression Scale (HAD)	14 items evaluating anxiety and depression; higher scores indicate more anxiety/depression
Rosenberg Self-Esteem Scale (RSE)	10 items each with a 4-point scale evaluating self-esteem
Mood Adjective Check List Short Form (MACL)	38 items evaluating three psychological domains (pleasantness, activation, calmness)
Self-Rating Anxiety Scale (SAS)	20 items with a 4-point Likert scale evaluating anxiety; higher scores indicate worse HRQOL
Centre for Epidemiologic Studies Depression Scale (CES-D)	15 items each with a 4-point Likert scale; higher scores indicate more severe depression
Kessler 10	10 items assessing psychological distress, each with a 5-point Likert scale; higher scores indicate better HRQOL
State-Trait Anxiety Inventory Short Form (STAI-6)	6 items with a 4-point scale used to evaluate anxiety
Disease or system-specific instruments	
St. George Respiratory Questionnaire Short Form (SGRQ)	50 items in 3 domains (symptoms, activity, and impacts) specific to respiratory illnesses and originally developed to assess patients with airways disease
World Health Organization's Quality of Life – HIV (WHOQOL-HIV)	Modified version of the WHOQOL-100 used for patients with HIV; higher scores indicate better HRQOL
DR-12	TB-specific quality of life score with 12 items each ranked on a scale of 1–3; higher scores indicate better HRQOL
MOS-HIV	35-item questionnaire validated to assess quality of life in HIV-infected individuals