



Cohort Study

Profile and histopathology features of top three cases of Extra Pulmonary Tuberculosis (EPTB) in West Nusa Tenggara: A retrospective cross-sectional study

Fathul Djannah^{a,*}, Muhammad Nasrum Massi^b, Mochammad Hatta^b, Agussalim Bukhari^c, Idyatul Hasanah^d

^a Department Anatomy Pathology, Faculty of Medicine, Universitas Mataram, Mataram, 83126, Indonesia

^b Department of Microbiology, Faculty of Medicine, Universitas Hasanuddin, Makassar, 90245, Indonesia

^c Faculty of Medicine, Universitas Hasanuddin, Makassar, 90245, Indonesia

^d Faculty of Health Sciences, Universitas Nahdlatul Wathan, Mataram, 83115, Indonesia



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ABSTRACT

Background: Tuberculosis (TB) is an infectious disease that might threaten life with a high incidence rate globally, especially in developing countries such as Indonesia. Although some TB cases are found in the lungs, the incidence of patients with extra-pulmonary TB infection also shows a significant number. However, these cases are still underreported, especially in Indonesia. Histopathological examination is one of the gold standards for diagnosing EPTB.

Materials and methods: This is a cross-sectional retrospective descriptive study. This study uses data from medical records and histopathological examination results of extra-pulmonary TB patients at two hospitals in West Nusa Tenggara between May 2010 and February 2020. The inclusion criteria for this study were patients diagnosed with EPTB histopathologically and had complete paraffin block. In addition, the exclusion criteria were patients with incomplete data in the medical record. The data recorded include gender, age, organ location, area of residence, and histopathological features.

Results: There were 1.817 cases of extra-pulmonary TB in West Nusa Tenggara from May 2010 to February 2020. The top three organs were from the neck (84.7%), breast (14.1%), and colon (1.2%), with a total of 1362 cases. Women dominate the top three cases of EPTB with 894 patients (65.7%) and in the age group 21–30 (28%). Central Lombok has the most EPTB patients (450; 33.07%). Microscopic examination revealed well-organized granulomas in 988 patients (72.6%) and poorly organized granulomas in 374 patients (27.4%).

Conclusion: The three most frequent cases of EPTB found in West Nusa Tenggara are cervical lymphadenitis TB, mastitis TB, and colitis TB, with the majority of cases being well-organized granulomas. Further studies dealing with better designs and larger sample sizes need to be considered. The results of this study are significantly needed to determine the intervention strategies to reduce morbidity and mortality due to EPTB.

1. Introduction

Tuberculosis (TB) is one of the top 10 causes of death globally and is considered the leading cause of infectious agents caused by the bacillus *Mycobacterium tuberculosis*. In 2017, this disease affected millions of people every year with a very high mortality rate, reaching 1.3 million deaths and infecting around 10 million people. This figure is equivalent to 133 patients per 100.000 population [1]. The incidence of TB in Southeast Asia is 44%, and the lowest proportion in Eastern Europe is

2.7%. WHO Global Report in 2018 states that Indonesia is also included in the 20 countries with the highest TB burden in the world and contributed about 11% of new TB cases in 2017 [1,2]. Data from the Indonesian Ministry of Health in 2018 reported that as many as 1,017,290 TB cases were found in Indonesia, and there were 19,247 TB patients in West Nusa Tenggara, which showed a significant increase from 2016 [3]. "End TB Strategy" milestones for 2020–2025 can eventually be achieved if universal health coverage is provided, including diagnosis, treatment, prevention services, and multisectoral efforts to address

* Corresponding author. Department Anatomy Pathology, Faculty of Medicine, Universitas Mataram, Jl. Pemuda No. 37, Mataram, 83126, Indonesia.
E-mail address: fdjannah354@gmail.com (F. Djannah).

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socioeconomic issues as risk factors for TB [1,2].

Although some TB cases are found in the lungs, the incidence of patients with extra-pulmonary TB infection also shows a significant number. However, these cases are still underreported, especially in Indonesia. The factors are possibly associated with EPTB, including young age, female gender, ethnicity (Asian and African), and human immunodeficiency virus (HIV) infection [1,2]. The combination of under-reporting and diagnosis of identified cases creates a gap in the number of new estimated and reported cases. This is also possible by underestimating or overestimating the number of such new cases. For example, in Indonesia, a national study found that in 2017, only about 80% of new cases were detected, with 41% remaining unreported [3].

Histopathological examination is the gold standard for diagnosing unusual diseases such as EPTB [4–6]. The diagnosis of EPTB is divided into two characteristics, namely, well-organized granuloma (WOG) and poorly organized granuloma (POG). WOG consist of necrotic material and epithelioid cells or giant cells of datia Langhans, whereas POG consist of necrotic material, histiocytes, or plasma cells [7,8]. The incidence and characteristics of EPTB are very important. It forms the basis for planning and preparing treatment to provide the best management, take preventive actions, and increase research on EPTB. A fast and accurate diagnosis will speed up the start of treatment and help control the spread of TB so that it can indirectly decrease the morbidity and mortality of patients with TB [9,10]. This study aims to determine the profile and histopathological description of the three most frequent cases of EPTB in West Nusa Tenggara.

2. Methods

This study is a cross-sectional retrospective descriptive study. The data in this study were gained from the medical records of the West Nusa Tenggara Province General Hospital and Siti Hajar Hospital of West Nusa Tenggara. The data were collected from reports on histopathological examination results of patients who underwent surgery from May 2010 to February 2020. The inclusion criteria for this study were patients who had been diagnosed histopathologically with EPTB and had complete paraffin block. While the exclusion criteria for this study were incomplete patient data recorded in the medical record. The completeness of recorded patient data includes gender, age, location of the organ, patient’s residence area, and histopathological examination results. This study has been reported in line with the STROCSS criteria [11].

The research was approved by the ethics committee of the Faculty of Medicine, Universitas Mataram on July 29, 2021, with the number 232/UN18.F7/ETIK/2021. This research has also been registered in the Research Registry with the number ‘researchregistry7538’.

3. Results

There were 1817 EPTB patients during the study period. The three most common EPTB organs were the neck, breast, and colon. The number of EPTB cases in these 3 organs was 1362 patients. Of the 1362 patients, most were women, namely 894 patients (65.7%), and the majority were in the 21–30 age group (26.2%). Most EPTB patients came from the Central Lombok region, which was 33% of all EPTB cases in West Nusa Tenggara (Table 1).

Based on Fig. 1 shows that the three most cases of EPTB in West Nusa Tenggara from May 2010 to February 2020 are cervical lymphadenitis TB in 1153 patients (84.7%), mastitis TB in 193 patients (14.1%), and colitis TB in 16 patients (1.2%).

It is seen based on Fig. 2 that the three most cases of EPTB had microscopic features in the form of WOG, which was dominated by necrotic materials, epithelioid cells, datia Langhans giant cells, and histiocytes cells (see Figs. 3 and 4).

Histology features of WOG consist of necrotic materials. It is surrounded by epithelioid cells, mature lymphoid cells, and datia langhans giant cells. At the same time, histology features of POG consist of

Table 1
Distribution of gender, age, and area location of EPTB patients.

Category	Sub Category	Value %
Sex	Male	468 (34,3%)
	Female	894 (65,7%)
Age	0–10	115 (8,4%)
	11–20	288 (21,1%)
	21–30	358 (26,2%)
	31–40	281 (20,6%)
	41–50	139 (10,2%)
	51–60	64 (4,6%)
	61–70	44 (3,2%)
71–80	11 (0,8%)	
Location	North Lombok	78 (5,7%)
	Mataram	189 (13,8%)
	Central Lombok	450 (33%)
	West Lombok	121 (8,8%)
	East Lombok	123 (9%)
	Sumbawa	182 (13,3%)
	Dompu	134 (9,8%)
Bima	85 (6,2%)	

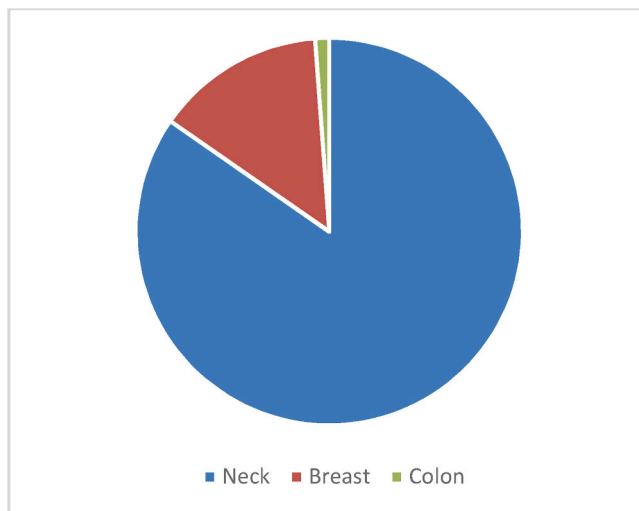


Fig. 1. Organ location of top three cases of EPTB.

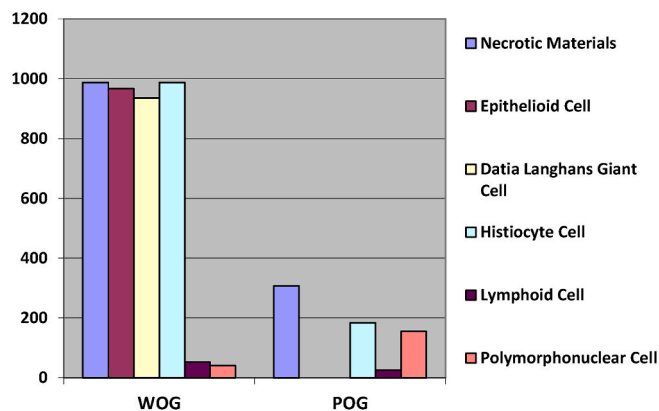


Fig. 2. Microscopic features of top three cases of EPTB.

necrotic materials, histiocyte cells, mature lymphoid cells, or polymorphonuclear cells without epithelioid cells or datia Langhans giant cells¹²⁻¹⁵. In the microscopic examination, it showed WOG in 988 patients (72.6%) consisting of necrotic materials in 988 slides (72.6%), epithelioid cells in 966 slides (70.9%), histiocytes cell in 988 slides

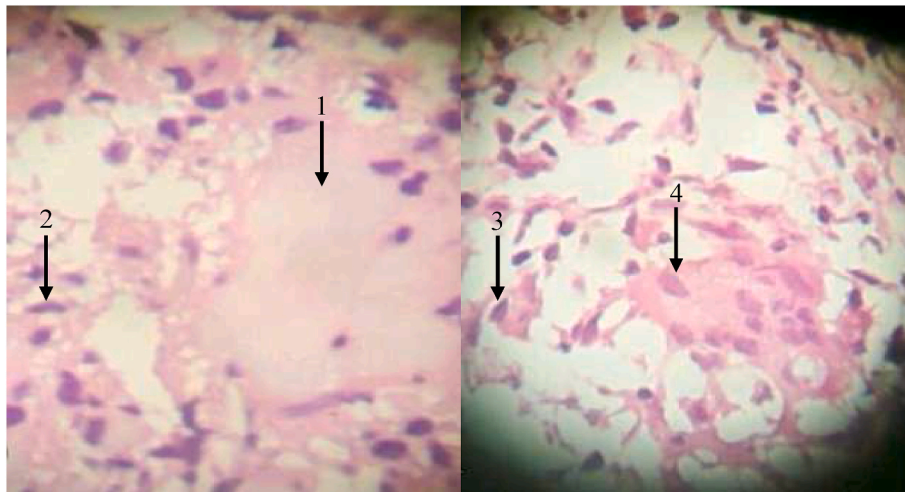


Fig. 3. Histology features of WOG (magnification 100x; H&E staining) consist of necrotic materials (1) surrounded by epithelioid cells (2), mature lymphoid cells (3), and Datia Langhans giant cells (4).

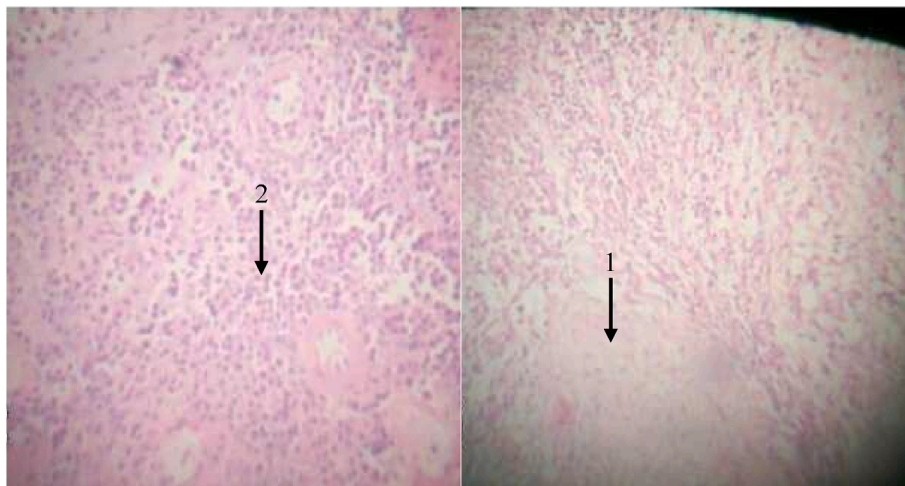


Fig. 4. Histology features of POG (magnification 100x; H&E staining) consist of necrotic materials (1), histiocyte cell (2), mature lymphoid cells (2), or polymorphonuclear cells without epithelioid cells or Datia Langhans giant cells.

(72.6%), giant cell datia Langhans in 935 slides (68.6%), polymorphonuclear cells in 53 slides (3.8%), lymphoid cell in 40 slides (2.9%). POG found in 374 patients (27.4%) consist of necrotic materials in 307 slides (22.5%), epithelioid cell in 0 slides (0%), histiocyte cell in 183 slides (13.4%), giant cell datia Langhans in 0 slides (0%), polymorphonuclear cells in 25 slides (1.8%) and lymphoid cell in 155 slides (11.3%).

4. Discussion

Extra-pulmonary tuberculosis (EPTB) is a bacteriologically or clinically diagnosed TB case involving organs other than the lungs, such as the pleura, lymph nodes, abdomen, genitourinary tract, skin, bones, joints, and the lining of the brain. In Indonesia, patients diagnosed with pulmonary and extra-pulmonary TB are notified or recorded and reported as cases of pulmonary TB. Based on the Regulation of the Minister of Health of the Republic of Indonesia in 2019 regarding the management of TB in Indonesia, the diagnosis is made based on one specimen with positive culture/microscopic/molecular tests or histology or strong clinical evidence consistent with extra-pulmonary tuberculosis and followed by the clinician's decision to start anti-tuberculosis therapy [12]. However, EPTB cases are still underreported in Indonesia, which has

reached 58% [1].

The results of this study indicate that gender that remained the most is female (56.3%). This study is in accordance with several previous studies. The factors that cause the incidence of EPTB in women to remain higher than men are due to the increasing number of women who go to work. There is an increase in social relations, which might raise cases of oropharyngeal exposure to MTB. Genetic and hormonal factors also influence. In addition, there are differences in treatment when women tend to prioritize their sick family over themselves in seeking treatment, and it is often done when conditions are severe [13–15].

This study sample's majority age was 21–30 years with 382 patients (28%). This is similar to the research conducted by Salvador et al., 2015 [13] and Yu Pang et al., 2019 [15] where most of the research distribution is aged 21–30 years (40%). The results of this study are also in line with the research of Snow et al., Kamal et al., Simon et al. and Jeel Moya-Salazar, which stated that the incidence of EPTB is less in old age [16–19]. Yu Pang in China stated that the prevalence of EPTB decreased significantly with the increase of age, whereas in pulmonary TB, it was the other way around. This study explains that pulmonary TB is more common in old age due to changes in the body's immune system during ageing. It was also mentioned that the decline in macrophage function

occurred in the elderly and inflammatory cytokines produced by mononuclear cells were higher in the elderly (80.8 ± 2.1 years) than in the younger people [15].

Monocytes or macrophages are cells that initiate a cell-mediated immune system during TB infection, where MTB will be phagocytized, and the process of granuloma formation occurs [7,8]. The effect of lymphocytes can be seen from a study that compared the cytological features of cervical lymphadenitis TB in HIV-positive and HIV-negative people. It was found that POG and caseous necrosis were less common in the HIV-positive population. It is also believed to correlate with low CD4 cell counts in the HIV-positive population, where T-cells are required for epithelioid granuloma formation [20,21].

EPTB is TB that can manifest outside the lungs and affect most organs in the body, including intestinal TB, bone TB, cervical lymphadenitis TB and others [13,15,19,22,23]. The results of this study indicate that the neck is the most significant site of EPTB. These data are consistent with studies conducted by Pollet et al. in Australia [18], Yu Pang et al. in China [15], Abdallah et al. in Sudan [24], and Al-Otaibi et al. in Saudi Arabia [14]. The research results by Djaharuddin et al., in 2020 in Indonesia also strongly support the results of this study, where intestinal TB is one of the three largest EPTB cases [22].

The results showed 988 patients (72.6%) with organized granulomas. This result is similar to the study conducted by Park et al., which stated that histopathological features of well-formed granulomas were the most frequently collected samples [25]. Lestari (2016) and Bagdia (2018) mention "suggestive TB" for histopathological features consisting of necrotic material, epithelioid cells, and datia Langhans cells [26,27]. These results are in agreement with our data showing that well-organized granulomas consist of necrotic material (988/988), epithelioid cells (966/988), and datia Langhans cells (935/988).

There is no consensus on which sampling method should be performed first when EPTB is suspected. Different procedures for obtaining samples have different sensitivities, and excisional biopsy is considered the most sensitive and the least invasive. Fine Needle Aspiration Biopsy (FNAB) is increasingly used worldwide as a first diagnostic step because of its simplicity and safety.

Early diagnosis and immediate treatment are at the forefront of reducing the incidence of lymphadenitis TB and other TB cases. The rise of awareness of health workers and the public about the common symptoms of cervical lymphadenitis TB will support Global End TB. The efficiency and accuracy of TB diagnosis will determine the success of treatment, the control of TB infection, and the determination of risk factors to prevent poor TB treatment outcomes in both pulmonary TB and EPTB [13,28]. It is also necessary to develop existing evaluation methods and procedures for preventing and detecting TB [28].

This study has several limitations, namely information from the requested form for anatomical pathology examination from the clinician and the histopathological examination results. Many doctors from various disciplines were involved, and various tests were carried out. However, not all of them were included in the clinician's request form for anatomical pathology examination. Selection bias may occur, partly because biopsies were performed by different surgeons, variation in clinical presentation, variation in size of lymphadenopathy, and different suspicions of tuberculosis etiology, especially in the poorly organized granuloma type.

A study with a better design and a larger number of samples is needed to determine patients' profiles and histopathological features with EPTB. This study can be used as a basis for determining the intervention strategies to reduce morbidity and mortality in EPTB patients.

5. Conclusion

The top three cases of EPTB in West Nusa Tenggara are cervical lymphadenitis TB, mastitis TB, and colitis TB, with most cases being well-organized granulomas. Further studies with better designs and larger sample sizes need to be considered. The results of this study are

needed as a basis for determining intervention strategies to reduce morbidity and mortality due to EPTB.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

This study was approved by the Health Research Ethics Commission, Faculty of Medicine, Universitas Mataram (232/UN18.F7/ETIK/2021).

Sources of funding

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Author contribution

FD and MNM conceived and designed the study, conducted research, provided research materials, and collected and organized data. FD and MH analyzed and interpreted data. FD and IH wrote the initial and final draft of an article. AB provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Consent

We have made an effort to remove any possible clues of identifying the patient. There is no ethical issue in this study as to our knowledge.

Registration of research studies

Name of the registry: Fathul Djannah.

Unique Identifying number or registration ID: researchregistry7538.

Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/register-now#user-researchregistry/registerresearchdetails/61dedb822787c80021326749/>

Guarantor

Fathul Djannah, MD.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.103318>.

References

- [1] World Health Organization, Global tuberculosis report 2018 [Internet] [cited 2021 Nov 17]. 265. Available from, <https://apps.who.int/iris/handle/10665/274453>, 2018.
- [2] World Health Organization, Improving the Diagnosis and Treatment of Smear-Negative Pulmonary and Extra-pulmonary Tuberculosis Among Adults and Adolescents Recommendations for HIV-Prevalent and Resource-Constrained Settings, 2007.

- [3] R.I. Kementerian Kesehatan, Laporan Nasional RISKESDAS 2018, 2019. Jakarta.
- [4] K.K. Shah, B.S. Pritt, M.P. Alexander, Histopathologic review of granulomatous inflammation, in: *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, Elsevier Ltd, 2017, pp. 1–12. Vol. 7.
- [5] I. Eldsoky, W.F. Ismaiel, A. Hasan, M.H. Abdelazim, A.A.A. Ibrahim, M.E. Alsobky, et al., The predictive value of nasolacrimal sac biopsy in endoscopic dacryocystorhinostomy, *Ann. Med. Surg.* (2021 May 1), 65.
- [6] A. Hasan, K. Nafie, K. Monazea, A. Othman, A. Salem, A. Ismail, A rare case of recurrent eccrine poroma underlying gluteal abscess, *Int. J. Surg. Case Rep* 75 (2020 Jan 1) 29–31.
- [7] L.G. Koss, M.R. Melamed, in: *fifth ed.Koss' Diagnostic Cytology and its Histopathologic Bases*, vol. 1, Lippincott Williams & Wilkins, 2006.
- [8] C.M. McClean, D.M. Tobin, Macrophage form, function, and phenotype in mycobacterial infection: lessons from tuberculosis and other diseases, in: B. Napier (Ed.), *Pathogens and Disease* vol. 74, 2016 Oct (7):ftw068.
- [9] M. Hatta, A.R. Sultan, N. Tandirogang, Yadi Masjudi, Detection and identification of mycobacteria in sputum from suspected tuberculosis patients, *BMC Res. Notes* 3 (1) (2010), 72.
- [10] T.A. Wikanningtyas, M. Hatta, M.N. Massi, I. Pratiwi, M. Fachri, S.S. Santoso, et al., Diagnosis of a spectrum of pulmonary tuberculosis at islam hospital sukapura, jakarta, Indonesia: a retrospective study of 317 cases, *J. Med. Sci.* 18 (3) (2018) 143–148.
- [11] G. Mathew, R. Agha, J. Albrecht, P. Goel, I. Mukherjee, P. Pai, et al., STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery, *Int. J. Surg. Open* 37 (2021 Dec 1), 100430.
- [12] R.I. Kementerian Kesehatan, Keputusan Menteri Kesehatan Republik Indonesia Tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Tuberkulosis. Kementerian Kesehatan RI, HK.01.07/MENKES/755/2019 Indonesia, 2019.
- [13] F. Salvador, I. Los-Arcos, A. Sánchez-Montalvá, T. Tórtola, A. Curran, A. Villar, et al., Epidemiology and diagnosis of tuberculous lymphadenitis in a tuberculosis low-burden country, *Medicine* 94 (4) (2015 Jan) e509.
- [14] F. Al-Otaibi, M. el Hazmi, Extra-pulmonary tuberculosis in Saudi Arabia, *Indian J. Pathol. Microbiol.* 53 (2) (2010 Apr 1), 227.
- [15] Y. Pang, J. An, W. Shu, F. Huo, N. Chu, M. Gao, et al., Epidemiology of extra-pulmonary tuberculosis among inpatients, China, 2008-2017, *Emerg. Infect. Dis.* 25 (3) (2019 Mar 1).
- [16] K.J. Snow, C. Sismanidis, J. Denholm, S.M. Sawyer, S.M. Graham, The incidence of tuberculosis among adolescents and young adults: a global estimate, *Eur. Respir. J.* 51 (2) (2018).
- [17] M.S. Kamal, M.H.E. Hoque, F.R. Chowdhury, R. Farzana, Cervical tuberculous lymphadenitis: clinico-demographic profiles of patients in a secondary level hospital of Bangladesh, *Pakistan J. Med. Sci.* 32 (3) (2016) 608–612.
- [18] S. Pollett, P. Banner, M.V.N. O'Sullivan, A.P. Ralph, Epidemiology, diagnosis and management of extra-pulmonary tuberculosis in a low-prevalence country: a four year retrospective study in an Australian tertiary infectious diseases unit. Gao L, editor, *PLoS One* 11 (3) (2016 Mar 10), e0149372.
- [19] J. Moya-Salazar, A.R. Nemolato, J. Samán, I.A. Pasco, J.M. Olivo-López, Extra-pulmonary and pulmonary tuberculosis among elderly Peruvian patients, *J. Immunol. Microbiol.* 2 (1) (2018), 4.
- [20] M. Farsida Hatta, I. Patellongi, Shabariyah R. Prihantono, R.A. Larasati Laras, et al., The correlation of Foxp3 + gene and regulatory T cells with scar BCG formation among children with Tuberculosis, *J. Clin. Tubercul. Other Mycobact. Dis.* (2020 Dec 1), 21.
- [21] R. Farsida Shabariah, M. Hatta, I. Patellongi, M. Prihantono Nasrum Massi, et al., Relationship between expression mRNA gene Treg, Treg, CD4+, and CD8+ protein levels with TST in tuberculosis children: a nested case-control, *Ann. Med. Surg.* 61 (2021 Jan 1) 44–47.
- [22] I. Djaharuddin, M. Hatta, N.A. Tabri, E. Muis, S. Safriadi, M.R. Primaguna, Intestinal tuberculosis: case series of three patients, *Respir. Med. Case Rep.* (2020 Jan 1), 29.
- [23] D. Mekonnen, A. Derbie, A. Abeje, A. Shumet, E. Nibret, F. Biadglegne, et al., Epidemiology of tuberculous lymphadenitis in Africa: a systematic review and meta-analysis, in: P.-J. Cardona (Ed.), *PLoS One* 14 (4) (2019 Apr 19), e0215647.
- [24] T.E.M. Abdallah, F.E.M. Toum, O.H. Bashir, T.I. Mansoor, M.M. Yuosif, M.A.-E. Elkhawad, et al., Epidemiology of extra pulmonary tuberculosis in Eastern Sudan, *Asian Pac. J. Trop. Biomed.* 5 (6) (2015 Jun) 505–508.
- [25] D.Y. Park, J.Y. Kim, K.U. Choi, J.S. Lee, C.H. Lee, M.Y. Sol, et al., Comparison of polymerase chain reaction with histopathologic features for diagnosis of tuberculosis in formalin-fixed, paraffin-embedded histologic specimens, *Arch. Pathol. Lab Med.* 127 (3) (2003 Mar 1) 326–330.
- [26] D. Lestari, B.M. Dewayani, A.H. Hassan, B.S. Hernowo, Pemeriksaan real time-polymerase chain reaction (RT-PCR) pada granuloma well organized dan poorly organized limfadenitis tuberkulosis, *Maj. Patolog.* 23 (2) (2014).
- [27] M. Bagdia, S. Bijwe, N. Hirani, A. Joshi, A. Chowdhary, M. Agrawal, et al., Lab diagnosis of extra pulmonary tuberculosis: comparison of Histopathology, cytology, ZeihlNeelsen stain and light emission diode microscopy with culture and nucleic acid amplification tests, *Int. J. Curr. Res. Rev.* 10 (2018).
- [28] P.F. Scheelbeek, A.J. Wirix, M. Hatta, R. Usman, M.I. Bakker, Risk factors for poor tuberculosis treatment outcomes in Makassar, Indonesia, *Southeast Asian J. Trop. Med. Publ. Health* 45 (4) (2014) 853–858.