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Bayesian analysis of multidrug resistance tuberculosis from Amravati Region using non-informative priors

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ABSTRACT

This study is an attempt to fit a binary logistic model on the data of TB- patients registered under DOTS from Amravati region, with the aim to determine predictors (risk factors) of MDR-TB, under Bayesian framework. Drug resistant tuberculosis is a serious public health problem in India and worldwide. Detection and treatment of MDR-TB is a priority in National Tuberculosis program in India. Bayesian approach with Non-informative prior is employed for data analysis in this study. MDR-TB presence is taken as the response variable in this study, with 18 explanatory variables related to clinical and treatment details of present and past history of the patients. Odds ratios for the Bayesian estimates of parameters are calculated using Gibbs Sampling procedure. It is found in the study that probability of developing MDR-Tb increases with increase in the number of previous TB treatment. Out of 18, eight variables are found to be potentially effective in the development of MDR-TB among TB patients.

Key Words: Multidrug-resistant tuberculosis (MDR-TB), Bayesian approach, Gibbs Sampling procedure, odds ratios.

Introduction

Poor TB treatment or incomplete Tb treatment often leads to Drug-resistant TB. TB bacteria that are resistant to the treatment with at least both first-line anti TB drugs isoniazid and rifampicin is named as Multi Drug Resistance tuberculosis (MDR-TB).[1] Worldwide Drug resistant continues to be a public health threat, in 2019 close to half a million people developed rifampicin-resistant TB (RR-TB).[2] The growing use of antibiotics in healthcare has led to increased prevalence of drug resistant bacterial strains.[3] MDR-TB is most worrisome form of TB infection as its treatment is challenging due to prolonged duration of therapy which involves drug toxicities and delayed diagnosis process. Morbidity and mortality rate by MDR-TB can be prevented by providing rapid diagnosis, proper guidelines and supervision and management of adverse drug reactions.[4] A Multi-country study indicated the importance of identification of the patients vulnerable to getting infection with MDR-TB strains among new cases and screening of the risk factors linked to MDR-TB.[5] The main causes of MDR-TB are improper treatment of sensitive TB patients, premature TB treatment interruption, and airborne transmission of resistant bacteria in public places.[2]

For assessing the risk factors or predictors of disease related data, logistic regression is preferred by most of the researchers. Development of binary logistic regression is most appropriate choice for predictive modeling.[6-13] The probability estimates can guide care providers as well as the individuals themselves in deciding upon further management[14]. The National Tuberculosis Elimination programme (NTEP) of India has achieved a remarkable milestone of significant increase in TB case notification in the year 2023, the Post Covid-19 pandemic; by implementing innovative strategies aimed at ending TB by the target year 2025. Program diagnosed 63939 cases of MDR-TB and highlighted the programme commitment to address drug resistant.[15] Thus, a reliable MDR-TB assessment is a need of time for better program management.

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Rationale of the Study

Many researches have been carried out in the field of statistics under prediction modeling to determine the risk factors for the emergence of TB or MDR. Most of the previous researches consider effects of socio economic and demographic factors in their work.

The systematic review and meta-analysis [9-16] is carried out for MDR-TB and its related factors highlighted the important facts that in India mostly smear positive TB is considered in the surveys excluding smear negative and extra-pulmonary TB, and TB treatment from private sector. TB Patients testing smear positive even after 3 months should be tested for drug-resistant TB. Whereas in present study in addition of current status and other demographic factors, details of the past- treatment history of tuberculosis patients is focused. In previous studies, mostly the risk History' is considered factor 'TB- as a categorical dichotomous variable indicating merely the presence or absence of TB history as (Yes/ No), however in this study new factors such as –

- Number of times patient undergone TB-treatment in past.
- Number of times a given type of outcome observed in the past and
- History number and TB- treatment week when patients were recommended for MDR-testing due to adverse drug reaction are included as continuous explanatory and categorical variables for prediction of MDR-TB.

Bayesian approach for prediction Modeling.

Prediction modeling has been carried out under Bayesian framework in the studies to present the result in more understandable form that is in terms of probability [17]. The advantage of Bayesian approach over classical is that it provide answers to specific scientific questions which single point estimate fails to cover adequately.[18]

In classical approach, the analysis of the logistic regression model is carried out using Maximum Likelihood Estimation (MLE) estimators. In the situation when MLE in small samples suffers from serious inferential problems in such cases the Bayesian approach has an advantage. Under Bayesian framework model parameters are estimated on the basis of their posterior distribution which is the combination of observed data and information from previous studies or personal experiences[17-18].

Objective of the Study

The objective of the present study is to identify the main risk factors effective for developing MDR-TB infection, using Bayesian approach modeling among TB patients registered under DOTS in Amravati region. In this paper, an attempt is made to deeply understand and study the effect of various clinical factors in detail from patients past TB-history record under Bayesian framework. The Bayesian logistic model has been used to analyze the impact of different risk factors (predictors) on patient's chances of having MDR-TB.

This study could be a guideline for TB clinicians and other policy makers in managing treatment for TB disease in patients with risk of MDR-TB infection. It could be helpful in preparing future plan for implementing MDR-TB treatment strategies in Amravati region.

Methodology

Study Design: In a cross sectional study, data of 650 tuberculosis patients are obtained from different DOTS centers, under Municipal Corporation Amravati region for the period of eight years from 2012-2019. Estimated population of MDR-TB patients undergone DST during this period is calculated as 1190. Data for MDR-TB diagnosed patients (n>30) from 12 PHU is collected using stratified sampling. According to global guidelines for the year 2012 the prevalence of MDR-TB is less than 3% amongst new cases and 12-17% in re-treatment cases in state of Maharashtra.

Using these prevalence values as a guideline sample size is verified by considering nearest values for the parameters in the sampling by using Cochran formula as -.

$$n = (Z^2 P (1-P) / d^2) / \{ 1+ (1/N ((Z^2P(1-P)/d^2) -1)\}$$

For total sample size n, where N as estimated number of Presumptive MDR-TB patients, d as 0.025 margin of error, P is the prevalence of MDR as 0.02 (1-3%) for new TB patients and prevalence as 0.145 (12-17%) for old TB patients. After performing simple computation with 95% Confidence level of standard normal distribution we get $\hat{n}$ = 575.

The variables selected for the study are demographic clinical and present and past treatment details of the patient. Patient's treatment cards and official records are used for this purpose.

Population and sample size: Population under study consists of patients who were registered under DOTS-TB program; for the year 2012 to 2019 in Amravati region. The present study mainly concerned with emergence of MDR. Only the presumptive MDR -TB patients are selected for the study who has undergone MDR- TB testing by any of the approved MDR-TB test after their routine TB-Test.[19] In Amravati region; exact numbers of isolates capable for DST could not be retrieved due to non-electrical storage of data for the selected period. So to be on a safer side sample size calculated by general Principal for logistic regression for this study (for 40 independent variables (Table-1) is determined by following a general principle that is EPV ≥10 for predictive modeling[8, 20] to avoid the problem of over fitting[8].Thus initially 650 samples are collected and sample size n= 402 of complete entries is selected for this study.

Ethics: Permission is obtained from the concerned Department by following proper procedure. Patients' data are kept strictly anonymous and confidential.

Variables of the study: Case definitions are obtained from the World Health Organization, Standard WHO definitions used by RNTCP to classify TB patients and TB treatment outcomes[21]. MDR is selected as an outcome Binary response variable, taking two values Multidrug resistance detected or not (yes, no) and 18 independent variables. Nine Discrete type of Variables selected for the study are- Age ,weight, 'Number of times patient took TB treatment in past', 'duration of the past TB treatment on totality (in days)', 'number of times patients result was cured , relapsed , complete/unknowns, defaulter, or failure in the past' . The categorical variables selected for the study and details of their categories are as given in Table-1. Last level of each variable in table-1 is considered as reference category.

Table-1: List of Categorical Variables selected for the study with detail of their categories

Gender	Female, Male
Type of disease	Pulmonary, extra-pulmonary
Smear Sputum result	Positive high, medium, low, negative
X-ray report	Stained/cavity present, clear
Tb detection by CBNAT	Positive, negative
Patient status at the Time of MDR testing	Relapse, failure, defaulter, Retreat, ongoing TB treatment suspended due to adverse drug reaction, new.
Suspect criteria	Any failure in past, Sputum positive follow-up of at least 4 months of previous DOTS course/ relapse/ defaulter, TB-patients having MDR contact, HIV positive TB patients, retreat ext tested positive by any/all of three test, New Sputum negative/ New extra pulmonary.
Regularity status in past treatments	Regular most of the time, irregular/frequent breaks/long gapes/ unknown
Transfer Code	History number and follow-up month when patients referred to MDR testing

Model Derivation: Construction of Classical Binary Logistic regression model for predicting the probability of MDR-TB for the above variables and its analysis is presented in detail in our previous work Singh et al. (2021),[22] all the details regarding evaluation of model fit (goodness-of-fit measures, comparisons using metrics AIC/BIC,

AUROC curve, R^2etc) are provided and model's reliability and overall performance was achieved in the paper. The logistic regression model is given as-

$$P(Y) = \log [(e^{\beta o + \ldots + \beta mXim} / 1 + e^{\beta o + \ldots + \beta mXim}) * (1 + e^{\beta o + \ldots + \beta mXim}]$$

Where *Yi (i=1,2,…,n)*~b (n, p_i) , (Y_i=1 ; if MDR-TB present in a patients and Y_i=0 ; if MDR-TB not present in the patient) with probability p_i. Thus, the Binary logistic regression model to identify β_j *(j= 1, 2, 3, ...m)* regression coefficient (risk factors) and constant term β_0 is:

$$P(Y) = \beta o + \beta_1 X_{i1} \ldots + \beta_m X_{im} \quad \ldots (2)$$

In present work, Binary logistic regression analysis is used to identify risk factors for predicting the probability of MDR-TB in Bayesian framework. P(*Y*) is the probability of given outcome to be predicted that is the probability of presence of MDR for X_j *(j= 1,2,3,...,m)*, explanatory variables.

Non-informative Prior Bayesian Model : The increased use of Bayesian methods in statistical analysis including logistic regression is due to its improved computational methods and capabilities which has made the use of Bayesian methods feasible in practice where other settings fails.[23] For the Bayesian analysis, prior information for all the parameters is required. Prior distribution is a product of likelihood function of observed data and information from previous studies.[24] The study on given data is carried out using non-informative and informative priors both and comparison is made in our later work. In the present work, to keep the paper length precise, it is assumed that no information is available about the parameters *(βo,..., βm)* therefore non-informative prior approach is adopted for this study. Two priors viz Non-informative Gaussian Prior and non-informative Uniform prior are selected for this purpose and posterior risk are obtained and compared for the model given by equation (2).

Non-informative Gaussian Prior: Normal distribution is the most common prior choice for logistic regression parameters [23]. The normal prior distribution with mean μ_j as'0' and large variance σ_j^2 (precision 0.0001) is selected for the parameters i.e. for all the coefficients given in equation-2. Then Bayes theorem is applied, to obtain the posterior distribution π (β_j/y) for *j = 0, 1, 2,..m*. It gives the product of likelihood function for the data, and marginal distribution for non-informative independent normal priors as -

$$\pi(\beta_j/y) \propto \prod_{j=0}^{m}\left[P(\beta_j\right] * \prod_{i=1}^{n}\left[L\left(\frac{\beta}{y}\right)\right]$$

$$= \prod_{j=0}^{m} \frac{1}{\sqrt{2\pi\sigma_j^2}} \exp\left\{\frac{-1}{2}\left(\frac{\beta_j - \mu_j}{\sigma_j}\right)^2\right\} \prod_{i=1}^{n}\left[\left(\frac{e^{\beta_{0+\ldots+\beta_m X_{i_m}}}}{1+e^{\beta_{0+\ldots+\beta_m X_{i_m}}}}\right)^{y_i} * \left(1 - \frac{e^{\beta_{0+\ldots+\beta_m X_{i_m}}}}{1+e^{\beta_{0+\ldots+\beta_m X_{i_m}}}}\right)^{(1-y_i)}\right] \quad \ldots \quad (4)$$

Non-informative Uniform prior: For non-informative Uniform prior, the maximum likelihood estimates of the logistic regression coefficients $(\beta_j), j = 0,1,2,\ldots,m$ obtained by classical logistic regression model are used as our prior beliefs. The posterior probability distribution under this prior is obtained by conducting the Markov chain Monte Carlo simulation.

The joint posterior density of β for Bayesian logistic regression considering uniform prior model is obtained by –

$$\pi(\beta_0, \beta_1, \ldots, \beta_m / \underline{y}) \propto \prod_{j=0}^{m} \left\{\frac{1}{\widehat{b_j} - \widehat{a_j}}\right\} * \prod_{i=1}^{n}\left[\frac{e^{y_i \sum_{j=0}^{m} \beta_j x_{ij}}}{\left(1+e^{\sum_{j=0}^{m} \beta_j x_{ij}}\right)}\right] \quad \ldots.(5)$$

Where, $\widehat{a_j}$ and $\widehat{b_j}$ are Maximum Likelihoods Estimates (MLE) from classical model (28) for a_j andb_j.

The conditional density of β given data when the complete data *{Yi}, i=1 … n* are available for both the Non-informative Gaussian prior (equation-4) and Non-informative Uniform prior (equation-5) is expressed in the standard format as below-

$$\pi(\beta_j/\underline{y})=\int_{-\infty}^{\infty}\dots\int_{-\infty}^{\infty}\pi(\beta_j/\beta_{\setminus j},\underline{y})\,\pi(\beta_{\setminus j}/\underline{y})\,d\beta_{\setminus j} \qquad \ldots.(6)$$

Then applying Bayes, theorem the marginal posterior for each regression coefficients β_j, is obtained by integrating β_j out from the joint posterior distribution for $j= 0,1,2,\dots,j-1,j+1,\dots,m.$

The expected value of the posterior probability distribution of parameter will be treated as regression coefficients of Bayesian logistic models. The standard form of the posterior distribution, given by Equation-6shows that prior does not belong to a conjugate family. Therefore the given integral, cannot be calculated explicitly. Thus a Markov Chain Monte Carlo (MCMC) Simulation method is required for obtaining the posterior distributions of the parameters of equation-4 and equation-5.

Analysis

Markov Chain Monte Carlo (MCMC) method is the most popular method of simulation from general posterior distribution[25]. Thus in this study posterior distribution for regression coefficients in equation-4 and equation-5, are obtained by using Markov chain Monte Carlo (MCMC) method. It generates Markov chains which give stationary (marginal) distribution equal to the posterior distribution of vector β**.** MCMC methods allow for sampling from a non-standard distribution; it uses Gibbs sampling procedure to simulate samples from the posterior distribution[25]. With the help of WINBUG software[25], standard MCMC methods, is carried out to fit the models obtained from non-informative Gaussian and uniform priors.

Table-2: Summary Statistics for Posterior distribution (Bayesian estimated values of the parameters for statistically significant categories using Non-informative Gaussian Prior).

Significant predictors	Mean ± SD	MC error	95% HPD		Odds Ratio for posterior means
			2.5%	97.5%	
Intercept	- 6.94 ± 0.97	0.01899	-8.749	-5.052	0.000967
CBNAT result (TB detected by CBNAT)	4.58 ± 0.85	0.01623	2.920	6.063	97.90523
Suspect Code (Sputum positive follow up after at least 4 mnths of DOTS:N/ relapse / defaulter)	0.92 ± 0.53	0.004833	0.081	2.073	2.549762
Suspect Code (TB patient having MDR contact)	5.27 ± 0.98	0.00703	3.478	7.336	194.4159
Suspect Code (HIV pos. TB)	1.75 ± 0.71	0.005405	0.486	3.204	5.725901
Suspect Code (Private referral patient)	2.11 ± 0.57	0.004731	1.124	3.33	8.231761
Suspect Code (New patient tested TB positive by any or all three test)	2.99 ± 0.61	0.006414	1.873	4.244	19.86580
No.TB treatment taken in past	1.33 ± 0.21	0.001318	1.019	1.804	3.769717
X-ray Test result (cavity /stained)	1.90 ± 0.33	0.002052	1.242	2.505	6.692583
Disease Type (Pulmonary TB)	-2.71 ± 0.56	0.006262	-3.842	-1.653	0.066670
Sputum Test result (Low TB bacteria)	1.21 ± 0.17	4.685E-4	1.007	1.634	3.350132
Sputum Test result (medium TB bacteria)	0.52 ± 0.28	8.318E-4	0.047	1.118	1.674642
Patient Status (relapse)	-1.29 ± 0.36	0.001263	-2.087	-0.741	0.274446
Patient Status (failure)	1.93 ± 0.58	0.005122	0.838	3.096	6.90330
Patient Status (ongoing TB treatment suspended due to adverse drug reaction first hist-first month)	0.31 ± 0.11	2.523E-4	0.203	0.602	1.369985
Patient Status (ongoing TB treatment suspended due to adverse drug reaction 2nd history 1st month)	2.13 ± 0.66	0.001782	0.818	3.346	8.38966
Regularity Status (patient did not take drug regularly frequent break/long gape in past)	0.73 ± 0.31	0.001395	0.129	1.339	2.064937

Analysis is carried out first, with the inclusion of significant factors (risk factors) which are determined by using the classical binary logistic regression model. For this analysis, Software SPSS version 22 is used, p-value of <0.05 is regarded as statistically significant predictor. The analysis of the logistic regression model is based on estimating parameters of the model through Maximum Likelihood Estimation (MLE). MDR-TB as the dependent variable Eight significant predictors (independent variables) are obtained as follows- Type of disease , Sputum result, X-ray result, CBNAT result, Suspect Code, Patient status, Regularity status, Number of Time TB-Treatment taken in past.

Win-bugs software is used in this study to apply Bayesian approach; it directly calculates the posterior distribution of parameters. Programming in Win-bugs is done to obtain Bayesian estimate of regression coefficients (β's) their standard deviation (±SD) and 90% highest probability density (HPD) interval for both the models derived by equation-4 and equation-5. These β coefficients are then used to obtain odds ratios. The result of the analysis is given in Table-2 and Table-3.

Table-3: Summary Statistics for Posterior distribution (Bayesian estimated values of the parameters for statistically significant categories Non-informative Uniform Prior)

Node	Mean ± SD	MC error	95% HPD		Odds Ratio for posterior means
			2.5%	97.5%	
Intercept	-7.212 ± 1.503	0.043	-10.63	-4.744	7.376
CBNAT result (Tb detected by CBNAT)	5.054 ± 1.38	0.047	2.89	8.229	156.647
Suspect Code (Sputum positive follow up after at least 4 months of DOTS/ Relapse / Defaulter)	1.123 ± 0.701	0.008	-0.234	2.518	3.074
Suspect Code (Tb patient having MDR contact)	5.14 ± 1.126	0.016	3.057	7.466	170.715
Suspect Code (HIV pos. TB)	1.559 ± 0.882	0.0126	-0.176	3.292	4.750
Suspect Code (Private referral patient)	1.856 ± 0.725	0.011	0.463	3.306	6.398
Suspect Code (New patient tested TB positive by any or all three test)	2.788 ± 0.775	0.011	1.318	4.344	16.248
No. TB Treatment Taken in past	1.495 ± 0.311	0.0028	0.9133	2.131	4.4593
X-ray T. result (cavity /stained)	1.778 ± 0.376	0.0038	1.066	2.543	5.918
Disease Type (Pulmonary TB)	-2.372 ± 0.675	0.0116	-3.719	-1.061	0.093
Sputum Test result (Low TB bacteria)	0.805 ± 0.338	0.0015	0.1474	1.473	2.236
Sputum Test result (medium TB bacteria)	0.434 ± 0.346	0.0016	-0.244	1.116	1.543
Patient Status (relapse)	-1.504 ± 0.48	0.0032	-2.462	-0.582	0.222
Patient Status (failure)	1.53 ± 0.726	0.0106	0.1262	2.979	4.618
Patient Status (ongoing TB treatment suspended due to adverse drug reaction second hist-1st month)	1.695 ± 0.852	0.0038	0.1703	3.524	5.446
Regularity Status (patient did not take drug regularly frequent break/long gape in past)	0.822 ± 0.351	0.0026	0.1411	1.517	2.277

Result

Very important step of Bayesian analysis is the convergence of MCMC, which indicates that algorithm is producing results from the target posterior distribution. Hence, monitoring the convergence of the algorithm is essential[26]. Most common and popular convergence assessment methods used in previous studies are employed here[23]. Using these methods the convergence of an MCMC is accessed for the parameters of statistically significant categories. Results from these diagnostic methods are given here only for strongest risk factors (Fig-1, Fig-2, and Fig-3) as the other factors also show same result.

Time series (history) plot: The Time series (history) plots for the statistically significant regression coefficient in both the model presents a good 'chain mixture' of two independently generated chains, which indicates the convergence of the two chains (Figure-1).

Density plot: Density plot for statistically significant regression coefficient in both the model are found to be smooth and uni-shaped which indicates convergence of parameter to the target distribution (Figure-2).

Gelman-Rubin statistic: The red line for Gelman-Rubin statistic is close to 1 on the y-axis it indicates convergence, which is clear from figure-3 in this study, as it touches 1 for all regression coefficients.

Monte Carlo standard errors: The convergence and measure of simulation accuracy are attained if Monte Carlo error for each of regression coefficients of predictor variables is less than 5% of its posterior standard error, this is also be verified from Table-2 and Table-3.

The Gibbs sampler algorithm is implemented with 111000 iterations in two different chains initialized at 0 (Chain 1) and 1 (Chain 2) for all parameters. The, 14000 burn-in terms are discarded for this analysis.

Figure-1: History Plot for Posterior distribution

Considering Gaussian Prior **Considering Uniform prior**

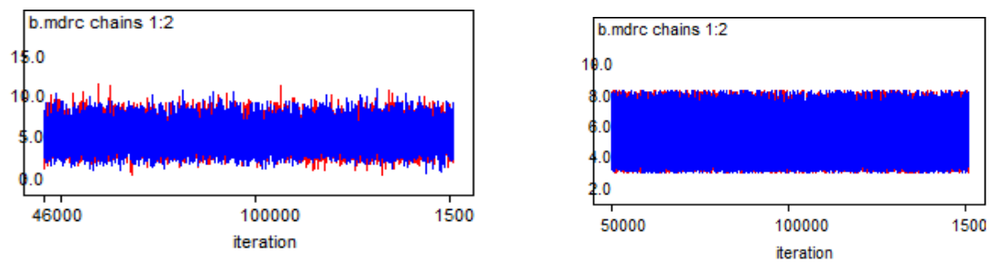
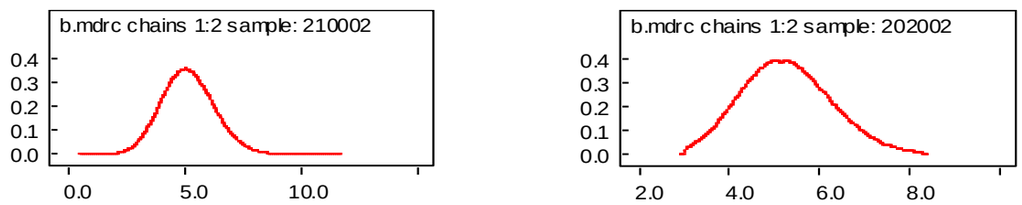


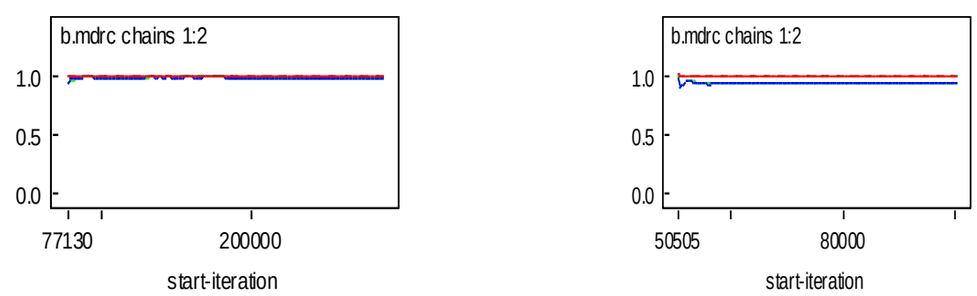
Figure-2: Density Plots test diagnosis for Posterior distribution

Considering Gaussian Prior **Considering Uniform Prior**



Figures-3: Gelman Rubin test diagnosis for Posterior distribution

Considering Gaussian Prior **Considering Uniform prior**



Discussion

The aim of the present study is to develop a valid statistical model for estimating the relationship between emergence of MDR-TB and other clinical factors among TB patients and to identify the significant risk factors (predictors) of MDR-TB under Bayesian framework.

The Study developed a valid statistical model, and identified the risk factors for MDR-TB. 15 Significant categories of predictors (risk factors) are obtained by using binary logistic regression analysis. Odds Ratios for these significant predictors (risk factors) are re-estimated using Bayesian analysis and their posterior risk with 95% HPD are calculated by using two different non-informative priors in two models.

The result obtained from this study confirms with the earlier studies which are irregular treatment and history of close contact with MDR-TB patients as the strongest risk factors for the development of MDR-TB, the lung cavities as a risk factor for MDR-TB and the likelihood of having MDR-TB increases as the total time of prior anti tuberculosis treatment measured in months increased [16, 27-28].

Bayesian estimated values of the parameters (mean) of significant risk factors and their odds ratio by both the non-informative priors are nearly same, with MC error by uniform prior is less for most of the risk factors. The result shows that regression coefficients of predictors 'type-of-disease' and 'patients-status' is negative with reference category, it means that probability of MDR-TB increases when level of type-of-disease and patients-status decrease. From Table-2 and Table-3; it is clearing that Probability of MDR-TB increases with the increase of level of other predictors andposterior of odds of MDR-TB are highest among the TB patients diagnosed by CBNAT-TB test. The posterior value of odd ratio of variable 'Number of time TB treatment taken in past' increase by one, then the odds of developing MDR-TB would be 1.5 (model-I) and 1.3 (model-II) times more. The posterior risk of developing MDR-TB is roughly 1.0 times more in irregular TB patients than the regular one. Whereas X-ray positive TB-patient is at 1.8 or 1.9 times higher risk than X-ray negative. Pulmonary TB patient and Sputum positive TB patient also have more risk of developing MDR-TB than Extra-pulmonary and TB negative patients.

This study also indicates that demographic factors like age, sex, weight and number of previous type-of-outcome does not play significant role in developing MDR-TB among TB patients. The Bayesian approach with non-informative prior is adopted in this study, the results of table-2 and table-3 are quite similar to what is obtained by frequents approach.[22]

Conclusion:

Result of this study support the decision suggested by WHO India TB report 2023.[2, 29] These decisions are as follows-

- MDR-TB diagnosis is offered to all patients who remain smear positive on any follow up including failures of first line treatment.
- CBNAAT is offered for TB diagnosis in key populations such as presumptive PLHIV, Children and EP-TB cases, and also to smear negative patients who have an X-ray suggestive of TB and patients referred from the private sector for early diagnosis of TB.

Since Multi Drug Resistant Tuberculosis testing is high burden on poor Economic countries, there is a tool-requirement for early detection of emergence of Multi Drug resistant among TB patient. For this it is a needed to detect high risk factors, which play important role in developing MDR among TB patients.

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