Evaluating risk factors in patients with severe asthma: a cross-sectional study

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Severe asthma (SA) is a major health problem which can be controlled with high doses of inhaled or systemic glucocorticoids. In this cross-sectional study, 96 patients with SA attending a pulmonary clinic in Rasht, Iran were included. They were identified based on the American Thoracic Society and European Respiratory Society guidelines. Data were collected from spirometry results, asthma control test (ACT), and depression anxiety stress scales. Among these 96 patients with SA, 69 were women (71.9%) and 27 (28.1%) were men. Mean age of patients was 54.5 ± 12.4 years. There was a significant relationship between gender and ACT score ($P = 0.03$). However, there was no significant relationship between depression severity and ACT score ($P > 0.00$). This study showed a significant relationship between anxiety and ACT score ($P = 0.008$). In addition, a significant relationship was seen between frequency of asthma exacerbation, stress, forced expiratory volume in 1 second (FEV1) and FEV1/forced vital capacity ($P < 0.05$). Thus there are many risk factors in our patients with SA including psychological disorders such as anxiety and depression which cause asthma exacerbations. The study also showed that increased sputum neutrophils are associated with asthma exacerbations.

Keywords: Psychological disorders, pulmonary function, risk factors, severe asthma.

ASTHMA is a common disease with airflow limitations due to inflammation, resulting in breathing difficulties, coughing and wheezing that may range from mild to severe. This may interfere with daily life and also be life-threatening[1]. More than 300 million asthmatic patients and 100 million more by 2025, pose a significant burden on healthcare systems. Around 250,000 worldwide deaths (4% of all deaths) from asthma have been reported[2–4]. The Global Initiative for Asthma (GINA) divides the severity of this disease into four groups, including mild intermittent, mild persistent, moderate persistent and severe persistent asthma[5]. Severe asthma (SA) requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic CS) to prevent it from becoming uncontrolled, or which remains uncontrolled despite organized therapeutic approaches[6–8]. The inducers of SA include various allergens, foods, drugs (salicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers), and occupational factors. Some effective cofactors include severe chronic sinus disease, gastroesophageal reflux, recurrent respiratory infections, relative immunosuppression and abnormal levels of immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM), hyperthyroidism, obstructive sleep apnea syndrome, psychological disorders and hormonal effects[6,7]. Patients with SA need regular daily dose of ICS (more than 1000 μg beclomethasone or equivalent dose of other ICS, the long-acting beta-agonist (LABA), theophylline, antileukotriene drugs and oral steroids[6]. Patients with SA may have a different patterns of inflammation (like neutrophilic asthma) and the involvement of distal parts of the airway. Therefore, a different response to anti-inflammatory drugs could be expected. Although effective treatment of majority of asthma patients who have eosinophilic inflammation is possible using ICS, it is more difficult to control patients with SA because a significant proportion have neutrophilic or other types of airway inflammation and may receive a higher dose of ICS or oral steroids[9–11]. The failure of asthma control is mostly related to lack of correct use of medications especially ICS, by patients because these drugs do not have any side effects. It is difficult to evaluate patients who use ICS, because there is no practical method for measuring the plasma level[12]. Patients with SA impose social and economic burden on the community[6]. In 2019, Fazlollahi *et al.*[13] reported that prevalence of SA in Iran was 3.9%, which was mainly observed in the higher age groups and male individuals[13]. In a study performed by Ayuk *et al.*[14] in Nigeria in 2018, the prevalence of SA was 8.7%. Several factors were associated with SA, including maternal smoking, pet cats, regular exercise and monthly paracetamol use[14]. In 2009, Lai *et al.*[15] showed that globally 6.9% of adolescents had SA symptoms, with range 3.8% in the Asia-Pacific and Northern and Eastern Europe, to 11.3% in North America. In this study[15], low-income countries were more at SA risk[15].

Considering the above, identification of patients with SA symptoms and factors associated with this disease, makes it easier for the disease to be controlled. In addition, social support programmes and regular management can help in the prevention of this disease. Therefore, we studied the frequency of risk factors of SA in a referral respiratory clinic in Guilan Province, Iran for better monitoring and control of the disease.

In this descriptive cross-sectional study between April 2014 and March 2015, patients with SA classified according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines, were considered. Inclusion criteria in this study were as follows: patients

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with diagnosis of SA, for at least one year, and patients with a history of reversible airflow obstruction as defined by ATS guidelines. The patients who did not have SA symptoms; such as medical, social or behavioural symptoms were excluded from the study. We collected the data, including age, sex, level of education, body mass index (BMI), history of previous disease, duration of asthma, daily activity status, family history of asthma, history of comorbidity (gastro-esophageal reflux, atopy, rhinosinusitis, etc.), occupational and environmental exposure, history of obstructive sleep apnea symptoms, use of other medications (such as salicylates, NSAID and ACE inhibitors), type and number of asthma medications, cell count (eosinophil, neutrophil, macrophage and lymphocyte) of sputum, serum total IgE level, hormonal status, health insurance condition, frequency of asthma exacerbation per year and duration of hospitalization due to asthma.

Sampling was done by the census method. Data were extracted from patients' files and the asthma control test (ACT) questionnaire (in Persian) was completed[6,13]. Pulmonary volumes and flows were measured using a spirometer (Jaeger) in sitting position and after appropriate training, and included pre- and post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC), FEV1 (per cent predicted), and FVC (per cent predicted). The serum total IgE levels were measured using ELISA (CinnaGen Company, Iran) method. Sputum samples were prepared with Giemsa stain to evaluate the percentage of inflammatory cells. The emotional status of patients was determined based on depression anxiety stress scale (DASS), and the diagnostic and statistical manual of mental disorders (DSM-IV-TR). The reliability of DASS was verified by the internal consistency coefficients and retest coefficients. Validation of depression and anxiety were confirmed by Beck's Depression Inventory (BDI) and four system anxiety inventory (FSAQ) scores. Data were analysed using SPSS version 21. Qualitative variables were analysed by chi-square and Fischer exact tests based on dual and multiple groups. Normal distribution of variables was determined based on the Kolmogorov–Smirnov test. To compare quantitative variables with normal distribution, the independent *t*-test and the one-way analysis of variance (ANOVA) were used in dual and multiple groups. The Mann–Whitney *U* test and Kruskal–Wallis test were used for the non normal distribution database. In this study, the significance level of the hypothesis test was determined as $P < 0.05$. The study was performed with informed consent and no additional cost to the participants.

Among 96 patients with SA, 69 patients were women (71.9%) and 27 patients (28.1%) were men. The mean and standard deviation (SD) of age was 54.5 ± 12.4 years, with a range of 25–84 years. There was no significant difference between ACT score, spirometry results and sputum cytology indices with age ($P \geq 0.05$). However, significant difference between sex and ACT score was observed with a higher score in females ($P = 0.03$). The mean of BMI in participants was 26.84, with 63.5% being higher than the normal range (BMI = 25). There was no significant difference between BMI and ACT, spirometry and sputum cytology indices ($P \geq 0.05$). Furthermore, there was no significant difference between occupation and cigarette smoking with ACT score and spirometry values ($P \geq 0.05$). In terms of associated disease, 53.1% of patients had positive history, 25.5% had hypertension (13 participants), 13.7% had hypothyroidism (7 participants), 13.7% had diabetes (7 participants), 11.8% had heart disease (6 participant) and sarcoidosis, tuberculosis, beta thalassemia minor and Churg–Strauss syndrome (1 participant). Relationship between history of previous disease and ACT and FVC showed that there was significant difference between ACT with using LABA + ICS ($P = 0.005$) and also between FVC and history of chronic sinusitis ($P = 0.004$) (Table 1). Also there was significant difference between chronic sinusitis with FEV1 ($P = 0.07$), use of antileukotriene with FEV1/FVC ($P = 0.003$) and non-nominal drugs with FEV1/FVC ($P = 0.05$). A significant difference between presence of associated disease and gastro-esophageal reflux disease with sputum neutrophilia was noted ($P = 0.05$ and $P = 0.07$ respectively). In addition, there was a significant difference between atopy and sputum eosinophilia in SA ($P = 0.06$). The eosinophilia was higher in patients with SA. Significant difference between the use of psychoanalytic medication and macrophage per cent in the sputum of patients was noted ($P = 0.034$) (Table 2). According to our results, there was significant difference between regular using of inhaler and ACT score ($P \leq 0.05$). Also significant difference was noted between regular use of drugs and ACT score ($P = 0.05$). Also, significant difference between severity of depression ($P = 0.05$), severity of anxiety ($P = 0.008$), severity of stress ($P = 0.037$) and ACT scores were noted (Table 3). The mean and SD of the duration of asthma was 12.30 ± 9.80 years with the range 1–48 years. We observed significant difference and correlation between the number of asthma attacks and severity of depression ($P = 0.02$ and $r = 237.0$). As show in Figure 1, we found that the increase in the intensity of the patient's depression was able to increase the number of attacks in patients with SA. Figure 1 also shows a significant difference and correlation between the number of attacks and anxiety scores ($P = 0.016$ and $r = 0.246$). There was also significant difference between the number of attacks and stress scores ($P = 0.014$ and $r = 0.25$). Furthermore, significant difference was noted between the number of asthma attacks and FEV1/FVC ($P = 0.017$) and FEV1 ($P = 0.029$).

In this study 96 patients with SA, most of them were middle-aged women. The ACT score was significantly highest in women, which could be due to more regular drug use, and also due to more their follow up. We do not found a significant relationship between the level of

Table 1. Comparison of asthma control test (ACT) score and forced vital capacity (FVC) scores based on drugs and related diseases

		ACT				FVC		
		Count	Mean	SD***	*P*-value	Mean	SD***	*P*-value
History of psychiatric medications	Yes	14	18.1	5.9	0.865	82.3	24.9	0.337
	No	82	17.9	4.7		89.1	24.4	
History of insurance	Yes	97	17.9	4.9	0.756	88	24.6	0.769
	No	5	18.6	5.2		91.3	22.6	
Underlying diseases	Yes	51	17.5	5	0.362	87	22.9	0.618
	No	45	18.4	4.7		89.5	26.2	
History of family asthma	Yes	47	17.6	4.9	0.503	87.4	25.8	0.758
	No	49	18.3	4.8		88.9	23.2	
History of atopy	Yes	60	18.3	4.7	0.349	91.1	24.4	0.121
	No	36	17.3	5.1		83.2	23.9	
History of chronic sinusitis	Yes	34	17.5	4.4	0.546	97.7	26.9	0.004
	No	62	18.2	5.1		82.9	21.5	
History of gastro-oesophageal reflux disease	Yes	55	17.7	4.6	0.568	87.7	25.1	0.871
	No	41	18.3	5.3		88.6	23.8	
LABA* + ICS**	Yes	94	17.9	4.8	0.005	88.2	24.6	0.873
	No	2	19.5	7.8		86	15.3	
ICS**	Yes	9	19.9	4.1	0.208	95.4	28.2	0.354
	No	87	17.7	4.9		87.4	24.1	
Oral prednisolone beta-Agonist	Yes	58	17.6	5	0.385	88.3	26.6	0.944
	No	38	18.5	4.7		87.9	21.1	
Oral theophylline beta-Agonist	Yes	9	20.1	4.2	0.160	86	33.2	0.786
	No	87	17.7	4.9		88.4	23.6	
Antileukotriene	Yes	30	17.1	4.7	0.258	86.5	24.9	0.661
	No	66	18.3	4.9		88.9	24.4	

*LABA, Long-acting beta agonist. **ICS, Inhaled Corticosteroids. ***SD, Standard deviation.

Table 2. Comparison of sputum macrophage and lymphocytes and total serum of IgE based on drug use and history of related diseases

			Macrophage			Lymphocyte			Total IgE		
		Count	Mean	SD	*P*-value	Mean	SD	*P*-value	Mean	SD	*P*-value
Psychiatric medication history	Yes	14	25.5	32	0.034	5	4.2	0.462	310.3	274.7	0.256
	No	82	7.9	16.1		8	9.8		214.9	194.8	
History of insurance	Yes	91	9	16.4	0.109	6.4	6.9	0.000	231.3	211	0.535
	No	5	27.3	47.3		26	20.8		154.3	51.4	
Underlying diseases	Yes	51	14.2	24.2	0.112	8.4	8.4	0.535	213.4	206.6	0.582
	No	45	5.3	9.1		6.7	10.4		244.7	208.5	
Family history of asthma	Yes	47	8.8	18.5	0.600	7.2	8.4	0.702	214.9	184.4	0.648
	No	49	11.8	20.4		8.2	10.5		240.6	230.8	
History of atopy	Yes	60	10.6	21.5	0.758	7.4	8.8	0.767	196.7	147.5	0.103
	No	36	8.7	11.6		8.3	11		294.9	256.5	
History of chronic sinusitis	Yes	34	7.8	19	0.482	7.1	7.6	0.735	230.5	177.1	0.927
	No	62	11.8	19.5		8	10.4		225.1	223.4	
History of gastro-oesophageal reflux disease	Yes	55	12.3	14.4	0.430	8.8	11.1	0.416	222.6	203.2	0.876
	No	41	7.9	12.2		6.5	7.2		231.4	212.4	

Table 3. Comparison of ACT and FVC scores based on severity of depression, stress and anxiety

		ACT				FVC		
		Count	Mean	SD	*P*-value	Mean	SD	*P*-value
Severity of depression	Normal	24	20.3	4.6	0.055	88.2	30.3	0.54
	Mild	10	17.7	4.7		89.6	22.7	
	Medium	30	17.8	4		86.2	23.2	
	Intense	11	16.8	5.3		99.5	19.2	
	Very intense	21	16.1	5.5		84.2	22.2	
Severity of anxiety	Normal	24	20.4	4	0.008	90.2	29.9	0.827
	Mild	6	19.2	5.5		82.5	24.6	
	Medium	25	17.1	4.3		86.8	20.2	
	Intense	13	19.1	4.5		94.1	30	
	Very intense	28	15.8	5.2		86.1	20.7	
Severity of stress	Normal	40	19.5	4.6	0.037	86.2	27	0.635
	Mild	12	17.3	3.2		86.5	16.7	
	Medium	19	17.7	4.6		91.5	25.9	
	Intense	19	16.4	5.2		93.3	23.9	
	Very intense	6	14.2	6.1		77.8	16.1	

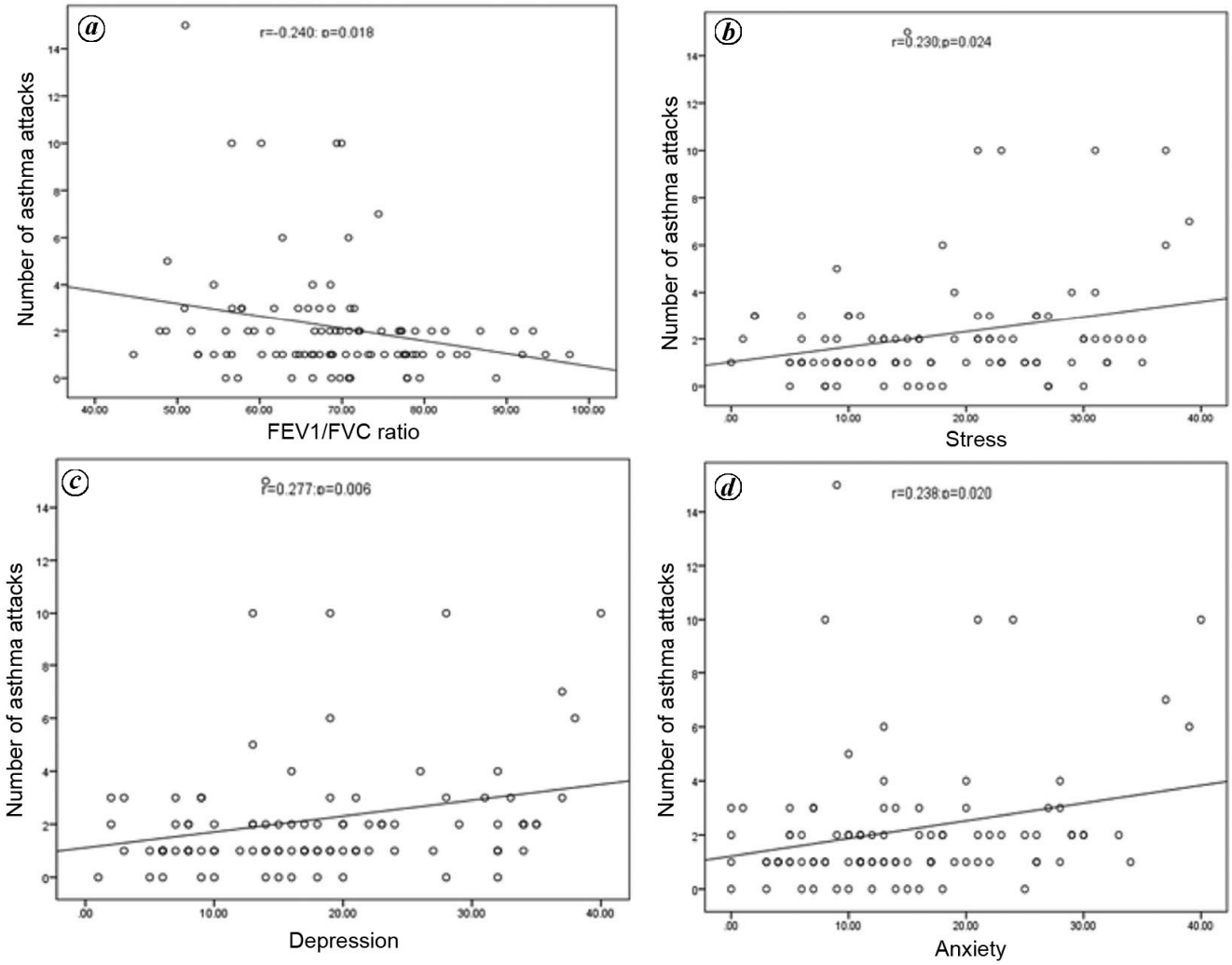

Figure 1. Correlation between (***a***) forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC), (***b***) stress, (***c***) depression, (***d***) anxiety and the number of asthma attacks.

education, age, occupation, BMI, cigarette smoking, alcohol consumption, and illicit drug use, ACT score, spirometric indices, and cytology of sputum. Interestingly, there was a significant difference between the number of asthma attacks and spirometric indices, including FEV1/FVC and FEV1. The study showed that a high percentage of neutrophils in the sputum of patients may be able to induce other types of inflammatory mechanisms and resistance to conventional drug therapy. Psychosocial assessment showed that patients with more anxiety had higher ACT scores. This may be due to more attention to the regular taking of medications by patients with more anxiety. There was significant difference between stress level and ACT score. In fact, individuals with normal stress score also had a higher ACT score. Furthermore, the study showed that the severity of depression has a significant statistical difference with the number of asthma attacks. This study showed significant relationship between stress score and the number of asthma attacks, but patients with normal stress levels also had more asthma attacks. This finding may be explained by both lack of accuracy in filling the questionnaire and a good and stable emotional condition during the interview despite some previous episodes of acute stressful events leading to asthma attacks. Melosini *et al.*[16] showed that in patients with uncontrolled asthma there was a significantly higher level of symptoms, medication use and peak expiratory flow (PEF) variability. They reported significant reverse relationship between ACT scores with patients' records of PEF. On the other hand, the present study does not show any relationship between ACT scores and biological markers. We also observed no significant difference between ACT scores and spirometric indices. These findings indicate that ACT scores could be related to symptom levels, appropriate use of medication and PEF variation during the four recent weeks and so can effectively describe the current level of asthma control[16]. Lavoie *et al.*[9] showed that the level of FEV1 was not related to severity of anxiety or depression. In the present study, there was no significant difference between spirometric indices and severity of anxiety, stress and depression. Di Marco *et al.*[10] showed that most asthmatic patients with depression were older and often obese (BMI > 30). In addition, they found a meaningful relationship between psychological characteristics, healthcare utilization, and emergency visits with anxiety, in patients who suffered from asthma[10]. Depression and anxiety disorders were independently related to the poor quality of life in asthma patients, and depression disorders were independently linked to low levels of asthma control. In addition, a tendency for more bronchodilator use was reported in people with anxiety (despite better asthma control) than those with depression disorders[10]. The relationship between psychiatric disorders and asthma can be explained based on the following hypothesis: First, psychological disorders like anxiety and depression may affect the perception of asthma symptoms and thus reduce the reaction of asthma control state. Secondly, uncontrolled or controlled asthma per se may lead to increased anxiety or depression[11]. Various factors can affect the risk factors associated with this disease. For example, in regions of the world with a poor health status and lower income, greater incidence of this disease is observed. Climate and geography are also considered as factors for this disease[15]. The age of the patients, their physical condition and severity of the disease are other factors to be considered, and all of these are due to differences in the results of different studies[14]. In fact, anxious may affect on severity of airway disorders, which could able to restrict asthma control. Lack of consent and collaboration by some patients to answer questions, inability to perform all laboratory tests by a single laboratory and a single technician, and also the inability to perform Esophageal cancer mentioning for definite diagnosis of Gastroesophageal Reflux Disease (GERD) can be considered as the limitations of our study.

Many risk factors such as old age, female gender, low level of education and illiteracy, housekeeping, higher BMI, associated illnesses and comorbidity, non-compliance to therapy, low ACT score and psychologic disorders have been considered in this study of SA patients. We found that patients who suffered from anxiety, stress, and depression had lower levels of FEV1, FVC, and FEV1/FVC, and septum neutrophils, which had correlation with number of asthma. With regard to correlation of ACT score and anxiety, depression in SA, we suggest that the quality of life and general health status of these patient would be improved by decreasing emotional problems which could increase their life expectancy.

Conflict of interest: The authors declare that they have no conflict of interest.

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Soil organic carbon pools under *Terminalia chebula* Retz. based agroforestry system in Himalayan foothills, India

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Knowledge of carbon (C) pools in soils is helpful in devising practices for efficient carbon management in intensive cropping systems. Carbon fractions of soil organic carbon are used as an indicator for land-use induced change in soil quality. The present study evaluated carbon pools under *Terminalia chebula* (chebulic myrobalan) based agroforestry system supplied with different nutrient sources, viz. farmyard manure, poultry manure, vermicompost, wheat straw and inorganic fertilizer (NPK @ 100 : 80 : 60). Carbon fractions, viz. very labile (C_1 *frac*), labile (C_2 *frac*), less labile (C_3 *frac*) and non-labile (C_4 *frac*), were analysed at 0–15 and 15–30 cm soil depth. The higher value of C_1 *frac* (13.8%), C_2 *frac* (4.8%), C_3 *frac* (8.3%) and C_4 *frac* (11.1%) were recorded under agroforestry as compared to open system. Among the nutrient sources, all the carbon fractions were higher under 100% integrated nutrient sources as compared to controlled treatment. Microbial biomass carbon (MBC) was recorded higher (298.31 μg g^{-1}) under agroforestry system compared to the open system (290.63 μg g^{-1}) at 0–15 cm. Among the different nutrient sources, higher MBC (458.66 μg g^{-1}) at 0–15 cm and lower (340.59 μg g^{-1}) at 15–30 cm soil depth was recorded in 100% integrated treatment. Thus, agroforestry-based land-use types and integrated nutrient management are more efficient for soil health and carbon management in Himalayan foothills.

Keywords: Active pool, carbon fractions, labile, non-labile, nutrient sources, passive pool.

DIVERSIFICATION of existing farming systems by developing suitable agroforestry models will provide diversified products such as food, fibre, fodder, fruit, timber, etc. for local consumption. Agroforestry add to the sustainability of agriculture and help in its diversification to attain huge benefits per unit land when carefully selected and managed[1]. Agroforestry systems are known for higher soil carbon sequestration[2]. Tree-based systems contribute more carbon stock compared to grassland system[3]. The tree of *Terminalia chebula* is a moderate to large deciduous tree growing up to 30 m in height and trunk up to 1 m in diameter[4]. It is a fast growing species and commonly known as *Chebulic myroblans*. The tree is well known for tanning leather, dyeing cloth and medicinal uses. Because of the economic benefits associated, this tree is suitably grown as an agroforestry tree with different intercrops. Organic matter in soil (SOM) is measured as an important constituent of every terrestrial ecosystem; perhaps it is the most recognized indicator for soil quality[5]. SOM is comprised of a variety of materials ranging from extremely high decomposable material to labile organic carbon (OC) which is corresponds to the stabilized of OC[6]. The quantity and quality of SOM is effective under agroforestry due to the addition of carbon in the form of litter production, crop residues, production of root and its exudates as well as the losses of carbon through decomposition. Soil total organic carbon (TOC) includes various fractions, which consist of different quantities of organic compounds and are broadly grouped as active and passive pools. The active pool (labile and non-labile) mainly comprises microbial biomass carbon (MBC), whereas, the passive pool is a multifaceted

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