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# Effect of Methotrexate on Liver in Patient with Rheumatoid Arthritis

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## Abstract

***Background*:** Methotrexate helps your immune system from assaulting your body's cells by calming it down. This helps to lessen the inflammation that causes rheumatoid arthritis's swollen and stiff joints, psoriasis' thickened skin, and Crohn's disease's gut damage. Because of its powerful effectiveness and safety, In the treatment of rheumatoid arthritis, methotrexate (MTX) is used as an anchor disease-modifying anti-rheumatic drug (DMARD) (RA).Although MTX aids a huge percentage of RA patients, it is not without adverse effects. When treating rheumatoid arthritis patients with the MTX, wide a variety of adverse effects, from minor to severe, can occur, leading to therapy termination. One putative harmful effect of methotrexate on the due to a local folate deficiency, there is a reduction in hepatic folate stores and toxicity. When MTX used with other medications, further research is needed to improve efficacy while reducing adverse effects. The management of MTX therapy is also reviewed, as well as options for dealing with adverse effects that may arise. ***Objective:*** The purpose of this study was to see how methotrexate affected individuals after 6 to 12 months of treatment for rheumatoid arthritis. ***Methods:*** Data was collected at the Shalamar hospital, Pakistan, between January 2021 and June 2022. Non-Probability Purposive Sample is the sampling strategy used in this investigation. Following the assignment of a study subject, the research took around 6 months to complete. After giving their informed consent, 120 patients between the ages of 30 and 50 were involved in this study. Data will be acquired using data collection technologies when an informed written permission form has been completed. ***Result:*** In this study 120 Rheumatoid Arthritis patients were studied, with 64 males (53.3%) and 56 women (46.7%) having an average age of 40 to 45 years and a range of 30 to 50 years. took part in the study, as shown in the graph (Table 3). In this study, 4 patients are 30 to 35 years old and have a percentage of (3.3%), 18 patients are 36 to 40 years old and have a percentage of (15%), another age group is 41 to 45 years old and has a percentage of (47.5%), and the last age group is 46 to 50 years old and has a percentage of (34.2%), as shown in the table (Table 2). The (Table 5) indicates the usual range of LFTs before Methotrexate, which is completely normal with no fluctuation in LFT parameters. As demonstrated in (Tables 6 and 8) where we examine the before and after effects of Methotrexate on the basis of patient immunity in 79 patients, the values of LFTs alter and become higher in comparison to normal, with a percentage of (65.8%). We compare the impact of Methotrexate on the basis of Gender using cross tabulation, which shows that LFTs were high in 41 males (67.1%) and 38 females (64.9%), as indicated in (Table 10). Finally, we compare the effect of Methotrexate on the basis of age factor as shown in (Table 11). After MTX therapy, RA patients experienced gastrointestinal side effects such as nausea, vomiting, and diarrhea, implying that MTX therapy will definitely affect the LFTs level and, most likely, according to the current study, will raise the LFTs level in blood, which will be treated promptly before further serious complications arise. A timely follow-up will be advised to all patients with consistently high LFTs levels. ***Conclusion:*** In this study, we discussed rheumatoid arthritis and the effects of methotrexate on rheumatoid arthritis patients' lives. It would appear that methotrexate is gaining popularity in the treatment of rheumatoid arthritis. Although there is risk of infection & probable cancer, the hazards are much outweighed by the potential therapeutic benefits. We also talked about R.A. diagnostic procedures. We covered the many characteristics of this autoimmune condition as well as several diagnostic approaches in this study.

**Keywords:** Rheumatoid arthritis, Methotrexate, Adverse effects, LFTs, MXT.



## INTRODUCTION

The antifolate metabolite methotrexate (MTX) affects DNA replication, repair, and synthesis. It has anti-inflammatory and immunological modulatory properties, and it was first used for the treatment of RA and psoriasis in 1951. Chronic systemic inflammation, synovial hyperplasia, and cartilage/bone degeneration characterize rheumatoid arthritis (RA), which causes temporary or permanent disability, early death, and major socioeconomic burdens. Regrettably, the underlying cause of RA is still unclear. In the etiology of RA, genetic, environmental, immunological, hormonal, and viral factors all play a role, with immune system activation being the most critical factor in disease development. While there is currently no cure

for RA, advances in our understanding of the disease's path physiology may pave the way for next-generation RA treatments [1]. Despite the fact that liver failure and cirrhosis are uncommon in rheumatoid arthritis (RA) patients, there have been a few cases reported among RA patients on methotrexate (MTX). There are no prognostic factors, and the prevalence of such disorders is unclear. The advancement of less important histologic abnormalities of the liver, as well as eventual fibrosis is not uncommon with long-term treatment. We calculated the number of individuals who had long-term MTX therapy for RA and how many of them developed serious liver damage. We also did a case-control study on these people to see whether there were any prognostic signs for cirrhosis and liver failure [2].

However, it wasn't until the early MTX therapy became more popular as a treatment for RA in the 1980s. A few years later, it was fond that it had a high effectiveness and was significantly superior among patients with chronic and severe RA compared to placebo [3]. The Food and Drug Administration (FDA) approved MTX as a RA treatment shortly after that, in 1988. When MTX is begun early in the course of severe RA, it can achieve Clinical remission is nearly identical to that seen with other biologic therapies for the condition. Combining MTX with other biological anchor disease-modifying anti-rheumatic drugs (DMARDs) may also help patients achieve better results [4]. As a result of its excellent efficacy-tolerance ratio, MTX has established itself as a first-line antirheumatic drug that is extensively recommended by rheumatologists in a variety of nations [5]. The European League Against Rheumatism claims that (EULAR), a typical synthetic DMARD, ideally MTX with low-dose glucocorticoids should be used as the first line of therapy for RA. Not only did MTX improve the efficacy of biological DMARDs, but it was also discovered that the dosages of MTX were lower than those of other synthetic DMARDs [6]. These findings indicate why MTX has a distinct position and why it is considered in the treatment of RA, this is the first-line DMARD [7].

However, rather than inefficacy, the termination of MTX during therapy is owing to its toxicity. Side effects were found well before MTX were widely used for RA patients in 1958 [8]. GI problems, hepatic dysregulations, pneumonitis, hematologic abnormalities, infections, nephrotoxicity, and dermatitis are some of the most common adverse effects of MTX. Because of the lower dose, life-threatening adverse effects are uncommon in MTX's RA therapy [9], although some issues can arise and produce severe consequences hepatotoxicity, lung injury, and myelosuppression, independent of the dosage [10]. As a result, lowering toxicity or informing patients about hidden side effects might help RA patients get better results. The bulk of recently published studies on the efficacy or toxicity of MTX as a therapy for RA are hospital-based observations, with no systematic classification based on symptoms [11]. As a result, this study will aid clinicians and researchers in learning more about the un favorable side effects of MTX therapy in RA patients [12].

Pharmacology and Pharmacokinetics of MTX Understanding the drug's mechanism of action and metabolism is crucial for reducing MTX toxicity and increasing therapeutic effectiveness [13]. A number of pharmacological mechanisms for MTX activity have been postulated, including inhibition of transmethylation processes with polyamine accumulation [14], Purine and pyrimidine synthesis inhibition, adenosine release stimulation, and adenosine-mediated inflammation suppression, and reduction of antigen-dependent T-cell proliferation [15]. All of these processes might be involved in MTX's anti-inflammatory actions. Folylpolyglutamate synthesis catalyses the polyglutamation of MTX, which enters the cell through decreased folate carriers. After polyglutamation, MTX is retained in cells for lengthy periods of time [16]. Another popular notion is that MTX and its polyglutamates block potentially predominantly de novo nucleotide synthesis by blocking dihydrofolate reductase (DHFR) to diminish tetrahydrofolate cofactors and, eventually, to deplete cells [17]. As a result of the buildup of MTX polyglutamates (MTXGlu) and dihydrofolates, various enzymes involved in the purine biosynthesis pathway, such as DHFR and thymidylate synthase, were inhibited. Both strategies outlined above might be connected to the reduction of NF-B activity, according to a recent discovery that MTX could limit the activity of T cells as well as fibroblast-like synoviocytes. These pathways may explain why in the treatment of RA, MTX is successful [18].

Hepatotoxicity caused by MTX in the treatment of leukaemia was first described in 1966. In 1971, during the therapy of psoriasis, a side effect of MTX that caused impaired liver function was discovered. During the first two to four years of MTX treatment, the risk of hepatotoxicity in RA patients might be as high as 70%. Histological abnormalities in the liver biopsies of MTX patients included hypertrophy of stellate (Ito) cells, steatosis, and hepatic fibrosis. Elevated alanine amino transferase/aspartate aminotransferase (ALT/AST) enzymes were seen in 14-35 percent of RA patients treated with MTX. Although the specific mechanism by which MTX causes hepatotoxicity is unclear, it is thought to be linked to the drug's cellular pathways. There are a few possibilities, one of which is that MTX causes Ito cells to activate. When persistent liver injury triggers Ito cells, they transform into myelofibroblasts, it causes cell hypertrophy by releasing collagen and other matrix proteins like fibronectin. Another notion is that

excessive intracellular MTX accumulation, particularly MTXGlu, causes folate depletion, a crucial component of DNA synthesis. Furthermore, greater plasma homocysteine levels in RA patients using MTX may cause oxidative stress or cause the cell to go into cytotoxic mode [19].

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**Side Effect**

After the first year of treatment, over 20%–30% of RA patients stopped using MTX because of the side effects, according to the study. However the risk of side effects might last up to 5 years. A variety of major toxic responses have been identified, the most prominent of which are hematological, carcinogenicity, and hepatotoxicity; Nephrotoxicity, lung, and gastrointestinal problems are among the others. Although the risk of adverse effects may be slightly higher during the first six months of MTX therapy, long-term monitoring is essential because all side effects are permanent. As a result, knowing the mechanisms of diverse side effects might be useful in the future for both clinical prescription and drug usage research [22].

Impact of methotrexate on the liver of individuals who are already receiving rheumatoid arthritis medication is the subject of this investigation. In rheumatic individuals, this might be the primary cause of liver fibrosis and cirrhosis. And then we'll speak about the effects of MTX on the liver, as well as the several laboratory tests used to diagnose rheumatoid arthritis [23]. The RA-Factor and C - reactive protein are used to diagnose rheumatoid arthritis at first (CRP). Both rheumatoid arthritis and gout have a positive RA-Factor. As a result, we use a specialized test called Anti-CCP to diagnose rheumatoid arthritis. This research is useful for students who want to do more work or research on the RA [24].

## PATIENT AND METHOD

Data was collected at the Hospital Shalamar hospital Pakistan, between January 2021 and June 2022. Non-Probability Purposive Sample is the sampling strategy used in this investigation. Following the assignment of a study subject, the research took around 6 months to complete. After giving their informed consent, 120 patients between the ages of 30 and 50 were involved in this study. Data will be acquired using data collection technologies when an informed written permission form has been completed. Data will be collected using a data collection sheet and Performa. The variables on the data collection sheet will be used to collect data. The volunteers will be informed about the study's contents, and there will be no risk associated. The patient will be asked about their medical history, age, weight, and medical issues such as obesity, pain in minor joints, and hypertension. The first report of MTX-induced hepatotoxicity in the treatment of leukaemia was published in 1966. During the treatment of psoriasis in 1971, a side it was revealed that MTX has an influence on liver function. Over the first 2 to 4 years of MTX therapy, the risk of hepatotoxicity in RA patients might be as high as 70%.

**Evaluation of Disease Activity**

Patients were visited twice a week for the first two weeks, then once a month after that. When the best results have been achieved, evaluations are normally done every two to three months. At the majority of visits, the following information was recorded, morning stiffness, pain in relation to activity, number of uncomfortable joints, number and severity of swollen joints, functional ability, examiner's assessment of disease severity, assessment of improvement; and change in prednisone dosage.

**Inclusion Criteria**

- Patients between the ages of 30 and 50 who report to the hospital with any kind of rheumatoid arthritis or who have RA factor positive and anti circulated proteins are also present.

**Exclusion Criteria**

- Patients who have been using steroids for a long period are excluded from this research.
- Alcoholic
- Smokers
- Liver disorders e.g. liver cirrhosis

**Statistical Analysis**

On the basis of specified factors, the data was analysed. The study employs cross tables and frequency tables. SPSS was used to evaluate the pre- and post-effects of methotrexate on the liver in arthritic patients. The data will be tabulated and analyzed using SPSS version 21.

## RESULT

The study included 120 RA patients, 64 males (53.3%) and 56 women (46.7%), with an average age of 40 to 45 years and a range of 30 to 50 years, as indicated in the graph (Table 3). In this study, 4 patients are 30 to 35 years old and have a percentage of (3.3%), 18 patients are 36 to 40 years old and have a percentage of (15%), another age group is 41 to 45 years old and has a percentage of (47.5%), and the last age group is 46 to 50 years old and has a percentage of (34.2%), as shown in the table (Table 2). The (Table 5) indicates the usual range of LFTs before Methotrexate, which is completely normal with no fluctuation in LFT parameters. Only when Methotrexate treatment is utilised will LFTs have an effect. Methotrexate is an immunosuppressant, which means it suppresses the immune system. It helps to minimize inflammation by slowing down your immune system. It's used to treat inflammatory conditions including rheumatoid arthritis and autoimmune disorders.

As demonstrated in (Tables 6 and 8) where we examine the before and after effects of Methotrexate on the basis of patient immunity in 79 patients, the values of LFTs alter and become higher in comparison to normal, with a percentage of (65.8%). The LFTs will alter somewhat in 41 individuals, but not significantly, and their proportion will be around (34.2 percent).We compare the impact of Methotrexate on the basis of Gender using cross tabulation, which shows that LFTs were high in 41 males (67.1%) and 38 females (64.9%), as indicated in (Table 10) and that the remaining 120 patients were normal on the basis of Gender.

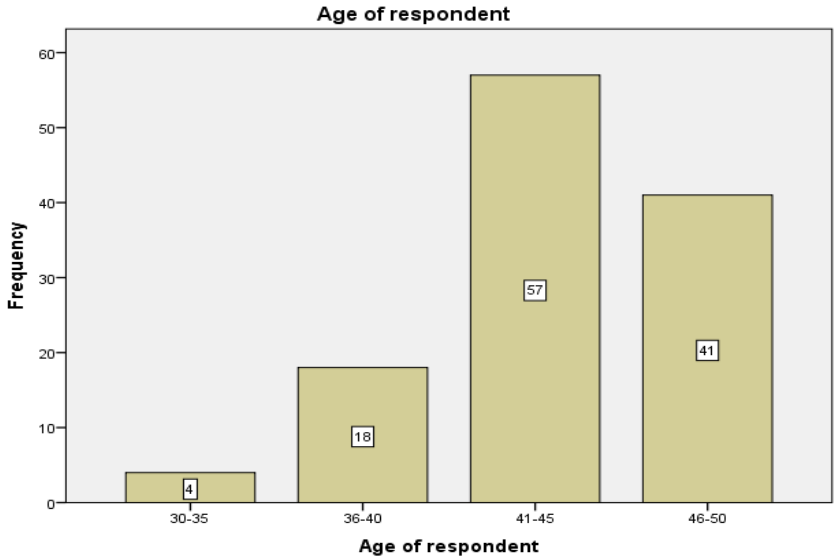
Finally, we compare the effect of Methotrexate on the basis of age factor, which shows that the level of LFTs was high in 3 patients aged 30 to 35 years, with a percentage of (75.0%), and in 14 patients aged 36 to 40 years, with a percentage of (77.8%). On the other hand, another age group of 41 to 45 years had 38 patients with a percentage of (77.8%).There were 24 patients in the final age group of 46 to 50 years old whose LFTs levels were abnormally high in contrast to normal, with a proportion of roughly 58.5 percent. The other patients in the whole population were normal, as indicated in the table (Table 11). MTX's bone marrow toxicity can be caused by a number of circumstances. Edelman *et al*., discovered that age is a risk factor for the development of MTX toxicity through an unknown mechanism. However, because no patient in this trial was above the age of 70, age did not found to be a significant influence in the development of thrombocytopenia. Impaired renal function, according to MacKinnon, appears to play a key role in MTX-induced pancytopenia. After MTX therapy, gastrointestinal side effects were common in RA patients, such as nausea, vomiting, and diarrhea, implying that MTX therapy will definitely affect the LFTs level and, most likely, according to the current study, will raise the LFTs level in blood, which will be treated promptly before further serious complications arise. A timely follow-up will be advised to all patients with consistently high LFTs levels.

**Table 1**

| **Statistics** | | | |
|---|---|---|---|
| | | Age of respondent | Gender |
| N | Valid | 120 | 120 |
| | Missing | 0 | 0 |
| Median | | 3.000 | 1.000 |
| Mode | | 3.0 | 1.0 |

**Table 2**

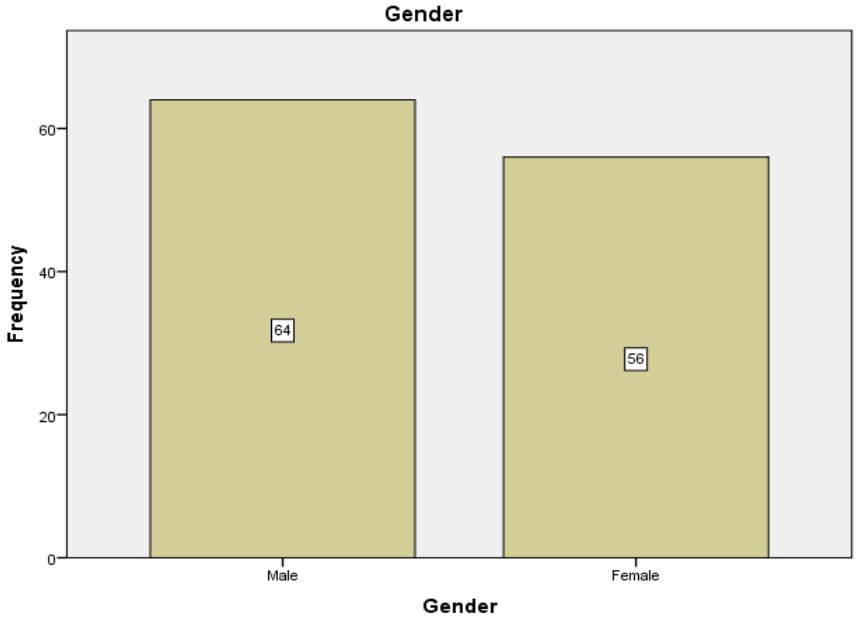
| **Age of respondent** | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | 30-35 | 4 | 3.3 | 3.3 | 3.3 |
| | 36-40 | 18 | 15.0 | 15.0 | 18.3 |
| | 41-45 | 57 | 47.5 | 47.5 | 65.8 |
| | 46-50 | 41 | 34.2 | 34.2 | 100.0 |
| | Total | 120 | 100.0 | 100.0 | |




**Graph 1**

**Table 3**

| Gender | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | Male | 64 | 53.3 | 53.3 | 53.3 |
| | Female | 56 | 46.7 | 46.7 | 100.0 |
| | Total | 120 | 100.0 | 100.0 | |



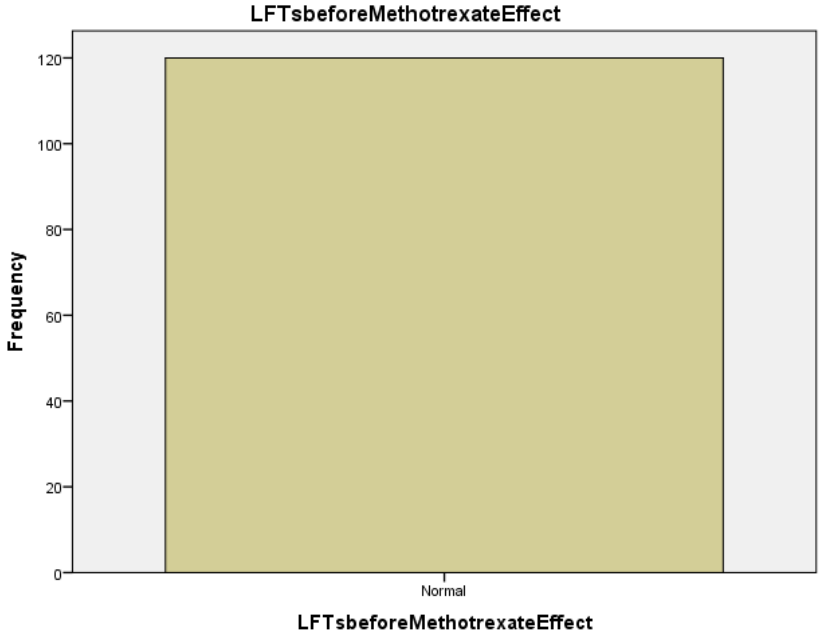

**Graph 2**

**Table 4**

| Statistics | | | |
|---|---|---|---|
| | | LFTs before Methotrexate Effect | LFTs after Methotrexate Effect |
| N | Valid | 120 | 120 |
| | Missing | 0 | 0 |
| Median | | 2.000 | 1.000 |
| Mode | | 2.0 | 1.0 |

**Table 5**

| LFTs before Methotrexate Effect | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | Normal | 120 | 100.0 | 100.0 | 100.0 |




**Graph 3**

**Table 6**

| LFTs after Methotrexate Effect | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | High | 79 | 65.8 | 65.8 | 65.8 |
| | Normal | 41 | 34.2 | 34.2 | 100.0 |
| | Total | 120 | 100.0 | 100.0 | |


**Graph 4**

**Table 7**

| Case Processing Summary | | | | | | |
|---|---|---|---|---|---|---|
| | Cases | | | | | |
| | Valid | | Missing | | Total | |
| | N | Percent | N | Percent | N | Percent |
| LFTs Before Methotrexate Effect * LFTs After Methotrexate Effect | 120 | 100.0% | 0 | 0.0% | 120 | 100.0% |

**Table 8:**

| LFTs Before Methotrexate Effect * LFTs After Methotrexate Effect Cross tabulation | | | | | |
|---|---|---|---|---|---|
| | | | LFTs After Methotrexate Effect | | Total |
| | | | High | Normal | |
| LFTs Before Methotrexate Effect | Normal | Count | 79 | 41 | 120 |
| | | % within LFTs Before Methotrexate Effect | 65.8% | 34.2% | 100.0% |
| Total | | Count | 79 | 41 | 120 |
| | | % within LFTs Before Methotrexate Effect | 65.8% | 34.2% | 100.0% |

**Table 9:**

| Case Processing Summary | | | | | | |
|---|---|---|---|---|---|---|
| | Cases | | | | | |
| | Valid | | Missing | | Total | |
| | N | Percent | N | Percent | N | Percent |
| Gender * LFTs After Methotrexate Effect | 120 | 100.0% | 0 | 0.0% | 120 | 100.0% |

**Table 10:**

| Gender * LFTs After Methotrexate Effect Cross tabulation | | | | | |
|---|---|---|---|---|---|
| | | | LFTs After Methotrexate Effect | | Total |
| | | | High | Normal | |
| Gender | Male | Count | 41 | 23 | 64 |
| | | % within Gender | 67.1% | 35.9% | 100.0% |
| | Female | Count | 38 | 18 | 56 |
| | | % within Gender | 64.9% | 32.1% | 100.0% |
| Total | | Count | 79 | 41 | 120 |
| | | % within Gender | 65.8% | 34.2% | 100.0% |

**Table 11:**

| Age of respondent * LFTs After Methotrexate Effect Cross tabulation | | | | | |
|---|---|---|---|---|---|
| | | | LFTs After Methotrexate Effect | | Total |
| | | | High | Normal | |
| Age of respondent | 30-35 | Count | 3 | 1 | 4 |
| | | % within Age of respondent | 75.0% | 25.0% | 100.0% |
| | 36-40 | Count | 14 | 4 | 18 |
| | | % within Age of respondent | 77.8% | 22.2% | 100.0% |
| | 41-45 | Count | 38 | 19 | 57 |
| | | % within Age of respondent | 66.7% | 33.3% | 100.0% |
| | 46-50 | Count | 24 | 17 | 41 |
| | | % within Age of respondent | 58.5% | 41.5% | 100.0% |
| Total | | Count | 79 | 41 | 120 |
| | | % within Age of respondent | 65.8% | 34.2% | 100.0% |

## DISCUSSION

Despite the fact that cytotoxic drugs have been used to treat rheumatoid arthritis for almost 30 years, they are still not widely employed, their mechanism of action in connective tissue illnesses is unknown. Methotrexate is a powerful anti metabolite because it prevents the formation of folic acid. It might work by inhibiting DNA, RNA, and protein production, immune suppression, anti-inflammatory effects, or other yet-to-be-discovered mechanisms. The current study

demonstrates the impact of methotrexate on the LFTs of methotrexate-treated patients. According to our current findings, before the methotrexate approach in Rheumatoid Arthritis, LFTs were normal, but after the process, the liver is affected, and LFT levels rise in relation to normal. Methotrexate's broad usage has been hampered by severe side effects, particularly hepatic. Significant liver damage has not occurred as a result of the use of pulse treatment and lower dosages, as well as the refusal of therapy to those with a history of liver illness or drunkenness. Due to a high occurrence of minor histologic alterations in liver biopsy specimens from these individuals, obesity and diabetes may predispose patients to a lower tolerance for methotrexate.

Weinstein looked at multiple prospective trials with a total of 309 individuals in which biopsy findings were evaluated before and after one to four years of psoriasis treatment with methotrexate. Cirrhosis occurred in about 3% of the patients in the first several years of treatment, according to these findings. It's possible that the lack of cirrhosis in any of our patients is related to the use of lower dosages than are typically used in psoriasis. It is widely known that mild to severe liver injury can be detected on biopsy before major changes in liver enzymes occur. The presence of rheumatoid factor in liver cells, as well as often lowered albumin levels, suggest that the liver is implicated in rheumatoid arthritis [25].

Methotrexate has been used to treat a variety of autoimmune illnesses for a long time. Given the concerns about methotrexate and liver side effects, it's not surprising that research into methotrexate's efficacy in autoimmune liver illnesses has taken longer than in other areas. Early cancer research revealed significant reductions in hepatic symptoms, as well as long-term damage in some cases. Age, obesity, and concurrent drugs, including methotrexate, appear to be risk factors for thiopurine-induced hepatotoxicity. From a pool of 1130 patients with RA who had taken MTX and had an elevated ALT/AST test, there were 132 MTX liver toxicity CASES (27.5%) and 38 of 120 CASES (31.7%) in the training set.

Although the alterations we observed are unlikely to be attributable to methotrexate medication, patients who exhibit them may be at risk for methotrexate- a liver damage that has been caused [26]. The role of leucovorin in avoiding methotrexate toxicity is unclear u71. Methotrexate does not appear to be carcinogenic, according to the research. Anti metabolites appear to be less likely than alkylating drugs to cause oncogenesis. Delayed wound healing and increased susceptibility to infection may be an issue, especially when corticosteroids are taken, however this was not found in this trial with the modest dosages utilized [27.

Determining whether liver damage in individuals with rheumatoid arthritis (RA) is a hepatic manifestation of the disease, related underlying liver disease, or hepatotoxic liver disease that arises during RA medication can be difficult. The most prevalent sign of RA liver damage is asymptomatic abnormal liver tests. In this study, the cumulative MTX dosage was discovered to be an independent predictor of MTX-related non-alcoholic fatty liver disease NAFLD with transaminases [28]. Furthermore, based on ALT levels, this variable revealed a significant dose-response connection with the severity of transaminases. The only independent predictor was the cumulative dosage of MTX, which was closely connected to ALT levels, which were suggestive of the severity of the transaminases [29].

Several researches have used anti-CCP1 and anti-CCP2 tests to investigate at the performance features of anti-CCP antibodies in RA. The anti-CCP1 test has a sensitivity and specificity of 44 to 56 percent and 90 to 97 percent, respectively. Anti-CCP antibodies were tested in patients with early arthritis who had been experiencing joint symptoms for less than six months. Many did not have an evident clinical diagnosis when they presented, but diagnoses were attempted later, generally 1–2 years after the initial presentation. The findings of tests were regularly withheld from physicians making clinical diagnoses. When compared to non-RA patients, anti-CCP antibody testing had a sensitivity of 39 to 50 percent and a specificity of 93 to 98 percent in those eventually diagnosed with RA [30].

## CONCLUSION

In this study, we discussed rheumatoid arthritis and the effects of methotrexate on the livers of RA patients. Methotrexate appears to be gaining traction in the treatment of rheumatoid arthritis. This group of people had a severe and resistant sickness. Perhaps an unselected sample might respond even better to methotrexate. We have observed that if a good response is not achieved after four to six months, continued therapy is rarely beneficial. This MTX is a fantastic medication for the treatment of RA and its side effects. Although there is a risk of infection and probable cancer, the hazards are much outweighed by the potential therapeutic benefits. We also talked about R.A. diagnostic procedures. We covered the many characteristics of this autoimmune condition as well as several diagnostic approaches in this study.

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