IMPRESSION OF IGG AND IGM ANTIBODIES IN AUTO-IMMUNE DISEASES V/S SEVERE COVID-19 INFECTION

Syed Jaffer[1]*, Juveria Siddiqua, Shifa Harmeen, Syed Muneb Ahmed, Hafsa Samreen and Anupama Koneru

[1]Assistant Professor, Department of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, Road no.3, Banjara Hills, Hyderabad, Telangana, India.
[2,3,4,5]Pharm D VI year, Department of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, Road no.3, Banjara Hills, Hyderabad, Telangana, India.
[6]Principal, Sultan-ul-Uloom College of Pharmacy, Road no.3, Banjara Hills, Hyderabad, Telangana, India.

*Corresponding Author: Dr. Syed Jaffer
Assistant Professor, Department of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, Road no.3, Banjara Hills, Hyderabad, Telangana, India. **Email Id:** syedjaffer@sucp.ac.in

ABSTRACT
The purpose of this study is to evaluate the impression of IgG and IgM antibodies in autoimmune v/s severe COVID-19 infection. The objectives were to compare the levels of IgG and IgM antibodies in autoimmune and COVID-19 infection and to study the relationship between the duration of disease and levels of IgG and IgM. It was a retrospective observational study, carried out in inpatient wards of Continental Hospitals, Hyderabad, for a period of 6 months. The laboratory parameters and pharmacotherapy details were collected in the pre-designed annexure form. This observational retrospective study was done among 67 patients in tertiary care hospital in Hyderabad. In this study, the total study population was divided into two groups –Patients diagnosed with at least one autoimmune disease (Group I). Patients diagnosed with Severe COVID-19 infection in our study (Group II). Infants and neonates are excluded from our study. significant difference was seen in the mean of IgG between group I and group II patients. The IgG levels were found to be significantly higher in autoimmune diseases when compared with that of severe covid-19 infections. The significant difference was seen in the mean of IgM between group I and group II patients. IgM levels were found to be significantly higher in autoimmune diseases when compared with that of severe COVID-19. We conclude that autoimmune diseases are more prevalent in women of child-bearing age. IgG and IgM levels were found to be increased with increase in severity in both autoimmune disease and coronavirus disease. Hence, IgG and IgM antibody test may be useful as effective predictors in diagnosis and severity of autoimmune disease and severe coronavirus disease.

KEYWORDS: Autoimmune, Covid-19, SLE, RA, IgM, IgG, Immune system.

1. INTRODUCTION

Autoimmune diseases are the third most common illness category, after cancer and heart disease, affecting approximately 8% of the population.[1,2] Previously, autoimmune diseases were considered to be rare but, through rigorous epidemiological studies, have now been shown to affect 3–5% of the population, with autoimmune thyroid disease and type I diabetes (T1D) being the most common autoimmune diseases. There are nearly 100 types of autoimmune diseases causing various types of immunological dysfunction, some of which affect just one organ, such as primary biliary cirrhosis (PBC), and some of which affect multiple organ systems, such as systemic lupus erythematosus (SLE).[3] In the United States, autoimmune diseases are among the leading causes of death in young and middle-aged women.[4]

Women are more prone to autoimmune diseases than men, with a female-to-male ratio of approximately 10:1 to 1:1 [except Crohn's disease, with a ratio of 1:1.2].[5] A number of differences have been reported between countries and ethnic groups that live in the same area and are at risk of specific autoimmune diseases. However, the pattern may not be consistent across autoimmune diseases. Certain ethnic groups might have a higher risk for some autoimmune diseases, while others may have a lower risk.[6] Natural polyreactive monoclonal antibodies (autoantibodies), which are derived from healthy subjects, bind to different antigens in a dose-saturable manner and to varying degrees.[7] These antibodies bind different antigens based on two types of epitope recognition[8,9], i.e., Recognition of the same or similar epitopes within the context of different antigens, or Recognition of different epitopes within the context of different antigens. The majority of natural autoantibodies are produced by (CD5+) B-1 cells. These B-1 cells

exhibit enhanced antigen presentation ability[10] and play an important role in the production of pathogenic autoantibodies in rheumatoid arthritis, Sjogren's syndrome, primary antiphospholipid syndrome, and systemic lupus.[11] Eighty percent of patients with active SLE have antibodies directed against dsDNA.[12] IgG antibodies are quite specific for SLE and are thus being used as diagnostic markers.[13,14] Although there is much information regarding IgG in the pathogenesis of SLE, the role of IgM antibodies is less established.[15]

Studies showed that IgM antibodies against dsDNA were common in SLE, as well as in rheumatoid arthritis, Sjogren's syndrome, and autoimmune liver diseases.[16] In normal adult murine or human serum, IgG natural antibodies can be observed when serum IgM has been removed or diluted.[17-20] A pathogenic IgG autoantibody induces a compensatory increase in IgM antibodies.[21] Pathogenic mechanisms unique to autoimmunity include antibodies against cell surface receptors that affect their function (i.e., myasthenia gravis), while in other autoimmune diseases, we can identify the same mechanisms involved in microbial defense (i.e., cell surface binding and lysis).[22] Any time an antibody responds to a soluble antigen, immune complexes are produced and cleared from the circulation by monocyte phagocytes.[23] The deposition of immune complex in the tissue as a cause of tissue damage is a common factor in SLE.[24]

In COVID-19 infection, there is an increase in virus-specific IgM during the acute phase, followed by an increase in virus-specific IgG later on.[25] In most of the patients, after 10 days of onset of symptoms, IgG or IgM antibody levels against SARS-CoV-2 nucleoprotein (NP) or receptor-binding domain (RBD) increased.[26] Another study found that SARS-CoV-2 virus-specific IgG peaked 17–19 days after the onset of symptoms, while virus-specific IgM peaked 20–22 days after the onset of symptoms. Another interesting observation was that the IgG and IgM levels in critically ill patients were higher than in mildly ill patients. Most severely ill patients showed cytokine storms, which are marked by high levels of pro-inflammatory cytokines in the serum. Additionally, IgG, IgM, and IgA specific antibodies against SARS-CoV-2. In COVID-19, high levels of acute phase reactants correlate with more severe disease.[27] In outpatient and inpatient settings, ESR is the most commonly used laboratory test. In this study, we aimed to investigate the prevalence of autoimmune diseases and compare the roles of IgG and IgM in autoimmune diseases and severe covid-19 infection.

2. MATERIALS AND METHODS
The study was conducted at Continental Hospitals Hyderabad, Telangana, India. It was a retrospective, descriptive, observational study conducted over the course of six months. A total of 67 subjects participated in this study, and they were split into two groups: 37 patients with autoimmune diseases, and 30 patients with severe COVID-19 infection. Patient data can be obtained through medical records. In our study, participants were divided into two groups based on inclusion criteria - Patients with autoimmune disorders (GROUP-I) and patients with severe cases of COVID-19 (GROUP-II). Infants and neonates were excluded. The study was started after the permission from the hospital authorities. In order to carry out the study, a patient profile form was designed, and all the relevant data were recorded in it from the case files and lab reports of the patients. The patient profile form was designed to include all the variables which were required for the study. Statistical analysis was carried out using the statistics software version 2007. All data was entered and saved to Microsoft Excel 2016 and data cleaning was carried out by professional statistician using SAS Software. The data was presented in the form of tabular columns and graphical representations. Chi-square test, Fisher's exact test, independent t- test, One-Way ANOVA were performed. There were no ethical issues as present study was a retrospective study based on existing patient medical records.

3. RESULTS
This observational retrospective study was done among 67 patients in tertiary care hospital in Hyderabad. In this study, the total study population was divided into two groups –
- Patients diagnosed with at least one autoimmune disease (Group I).
- Patient diagnosed with non-autoimmune (infectious) disease i.e., Severe COVID-19 patients in our study (Group II).

Infants and neonates are excluded from our study.

3.1. Demographics
The demographic features of the study patients are demonstrated in the following tables along with graphical representation.

3.1.1. Age
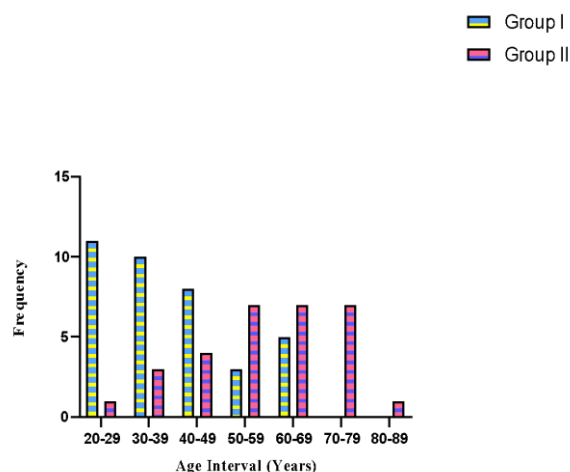The age distribution of Group I and Group II are tabulated as follows –

Fig. 1: Graphical representation of age distribution.

The statistically significant difference was found in the age between group I and group II patients. Autoimmune diseases are most common between 20-40 years of age whereas, non-autoimmune disease (severe COVID-19) is most common within the age group of 50-80 years with a P value of 0.0008.

3.1.2. Gender
The gender distribution of the Group I and Group II study participants is tabulated and represented as follows –

Table 1: Gender distribution.

Gender	Group I		Group II		P Value
	FREQ	%	FREQ	%	
Male	7	19	23	77	<0.0001
Female	30	81	7	23	

The statistically significant difference exists in the gender between group I and group II patients. Autoimmune diseases are most common in females whereas severe COVID-19 is most common in males with a significant P value of <0.0001.

3.2. Prevalence of autoimmune diseases
The prevalence of autoimmune immune diseases in the study population is graphically represented as follows –
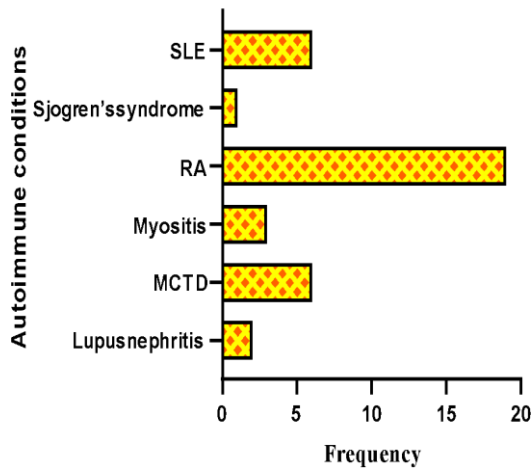
Fig. 2: Graphical representation of the frequency of autoimmune conditions in the study population.

Rheumatoid arthritis (51%) is the most common autoimmune disease seen in this study population, followed by Systemic Lupus Erythematosus (51%) and Mixed Connective Tissue Disorder (16%), which is then followed by Myositis(8%) and Lupus Nephritis(5%), and Sjogren's syndrome(3%) being the least common autoimmune disease in the subjects.

### 3.3. Subjective findings
3.3.1. Complaints
The common complaints which were experienced by the Group I (Autoimmune disease) patients and Group II (severe COVID-19 disease) patients are tabulated and graphically presented as follows –
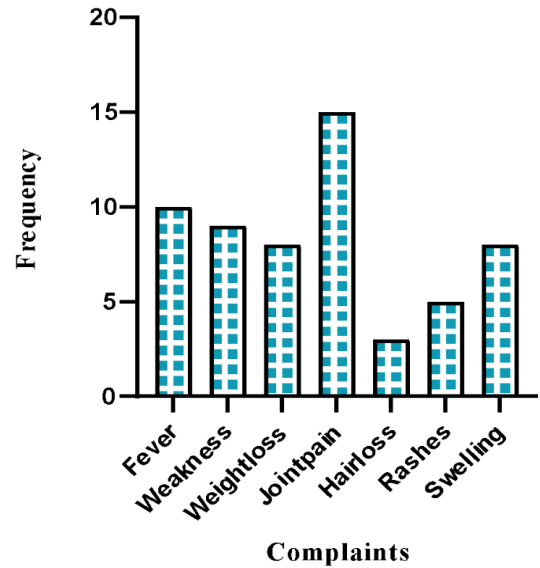
Fig. 3: Graphical representation of complaints experienced by group I patients

The common complaints experienced by the Group I patients are in the following order – Joint pain (as most of the subjects in our study population were diagnosed with RA), fever (27%), weakness (24%), weight loss (22%), swelling of joints (22%), rashes (14%), and hair loss (8%).
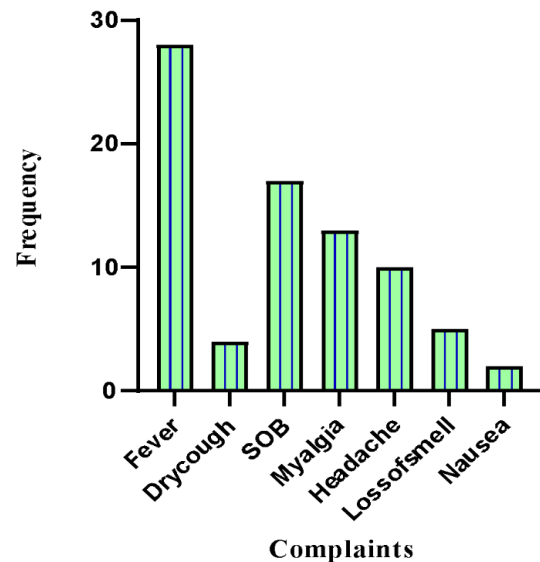
Fig. 4: Graphical representation of complaints experienced by group ii patients

The common complaints which are experienced by the Group II patients are in the following order – Fever (93%), SOB (57%), myalgia, (43%) headache (33%), loss of smell(17%), dry cough(13%), and nausea(7%).

3.4. Objective findings
3.4.1. Evaluation and comparison of igg levels between group i and group ii patients
The IgG levels are compared within the two groups by means of standard deviation. The comparison of IgG levels between Group I and Group II are tabulated and graphically presented as follows –

Table 2: Comparison of IgG between group I and group II

Variable	Group I	Group II	P Value
Minimum	1980	1620	
Maximum	2950	2150	<0.0001
Mean ± SD	2435±282.6	1825±161	

The table and graph stated above indicate that significant difference was seen in the mean of IgG between group I and group II patients. The IgG levels were found to be significantly higher in autoimmune diseases when compared with that of non-autoimmune diseases (infections) with a P value of <0.0001.

3.4.2. Evaluation and comparison of IgM levels between group I and group II patients
The IgM levels between the two groups are compared by means of standard deviation. The comparison of IgM levels between the Group I and Group II are tabulated and represented by means of graph as follows –

Table 3: Comparison of IgM between group I and group II.

Variable	Group I	Group II	P Value
Minimum	280	220	
Maximum	550	330	<0.0001
Mean ± SD	453.7±67.42	269.7±29.53	

The significant difference was seen in the mean of IgM between group I and group II patients. IgM levels were found to be significantly higher in autoimmune diseases when compared with that of non-autoimmune diseases (severe COVID-19) with a P value of <0.0001.

3.4.3. Evaluation and comparison of CRP and ESR between group I and group II patients
The CRP and ESR levels are evaluated and compared between the two groups by means of standard deviation. The comparison of CRP and ESR levels between the Group I and Group II are tabulated and graphically represented as follows –

Table 4: Comparison of CRP and ESR between group I and group II.

Parameter	Variable	Group I	Group II	P Value
CRP	Minimum	5.10	12.68	
	Maximum	102.2	95.30	0.0035
	Mean ± SD	29.06±3.31	45.57±4.45	
ESR	Minimum	20	18	
	Maximum	150	82	0.8757
	Mean ± SD	51.51±25.95	50.63±18.18	

The statistically significant difference was observed in the mean of CRP between group I and group II patients. The CRP was found to be significantly higher in Group II patients when compared with that of Group I patients with a P value of 0.0035.

There was no significant difference observed within the mean of ESR between the two groups. The ESR was found to be very slightly higher in Group I patients when compared with that of Group II patients with a P value of 0.8757.

3.5. Effect of duration of disease on IgG levels
The relationship between duration of disease and the levels of IgG of the two groups are tabulated and graphically represented as follows –

Table 5: Effect of duration of disease on IgG levels between group I and group II.

Group	Duration of Disease	IgG Mean ± SD	P Value
I	≤ 1 year	2256±302.1	
	1-3 years	2383±181	0.0037
	4-6 years	2641±281.3	
II	11-15 days	1691±41.21	
	16-20 days	1716±95.18	
	21-25 days	1977±91.60	<0.0001
	26-30 days	1988±94.32	

The statistically significant difference is observed between the duration of disease and the levels of IgG. The IgG levels increases as the disease progresses in both Group I and Group II patients with a significant P value of 0.0037 and <0.0001 respectively.

## 3.6. Effect of duration of disease on IgM levels

The relationship between duration of disease and the levels of IgM are demonstrated by means of standard deviation of the two groups, which are tabulated and graphically represented as follows –

Table 6: Effect of duration of disease on IgG levels between group I and group II.

Group	Duration of Disease	Mean ± SD	P Value
I	≤ 1 year	442.8±55.27	
	1-3 years	434.2±67.06	0.0840
	4-6 years	488.8±66.13	
II	11-15 days	255±23.30	
	16-20 days	254.4±21.86	0.0102
	21-25 days	288.6±27.34	
	26-30 days	290±29.66	

There is no significant difference observed in IgM levels as the disease progresses in Group I patients with a P value of 0.0840 whereas, within Group II patients, a significant difference exists within the IgM levels with the progression of disease with a P value of 0.0102.
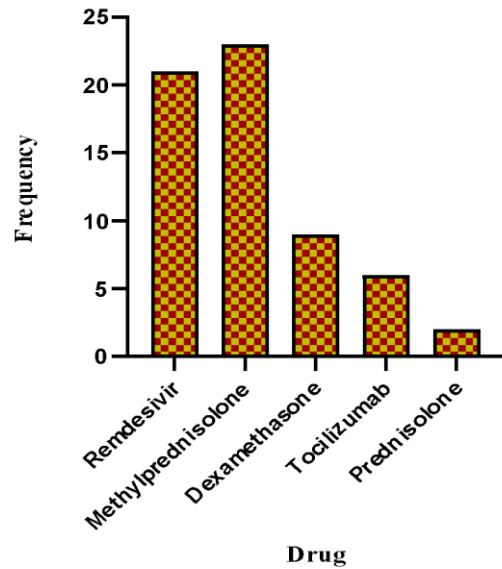
3.7. Commonly prescribed medications in group I patients
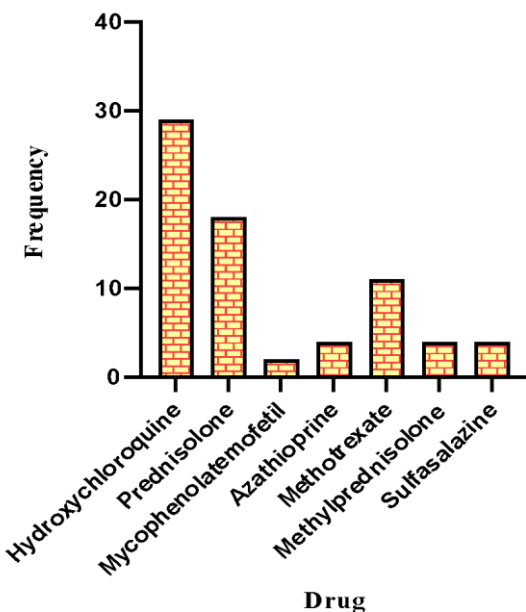
Fig. 5: Graphical representation of drugs prescribed in group I patients

The most common drug which is prescribed for autoimmune condition include Hydroxychloroquine (78%, followed by Prednisolone (49%) and Methotrexate(30%), which is then followed by Azathioprine(11%), Methyl prednisolone(11%), Sulfasalazine(11%), and Mycophenolate mofetil(being the least prescribed drug.

5.8. Commonly prescribed medications in group II (covid-19) patients

Fig. 6: Graphical representation of drugs prescribed in group II patients.

The most commonly prescribed drug for the management of severe COVID-19 disease include Methyl prednisolone (77%), followed by Remdesivir (70%), which is then followed by Dexamethasone (30%), Tocilizumab (20%), and prednisolone (7%).

4. DISCUSSION

In this study, the patients were divided into different age groups. In group I patients, the autoimmune disease is most common between the age group of 20-29 years (30%), followed by the age group of 30-39 years (27%). Studies done by other scientists strongly suggest that the onset of autoimmune disease most commonly occur during early adult life i.e., 15-40 years of age.[28] In this study, it is also clear that autoimmune diseases occur more frequently in females (81%) when compared to males (19%). The study conducted by researchers in 2014 suggest that increased immune reactivity in females might predispose them to develop autoimmune disease and gender differences in autoimmune disease may follow a female bias.[29]

In group II patients, the severe COVID-19 infection is most commonly observed within the age group of 50-80 years (69%), predominantly effecting male patients (77%). A systematic review and meta-analysis done in 2020 by other researchers reveal that COVID-19 male patients over the age of 50 years are at increased risk of severe disease and mortality when compared to female patients.[30]

In this study, the study data reveals that RA (51%) is the most commonly diagnosed autoimmune disease in the study population, followed by SLE (16%) and MCTD (16%). The population-based study on autoimmune

diseases conducted in Italy (2012) by other researchers show that autoimmune thyroiditis is the most common disease, followed by RA, psoriasis, and SLE.[31]

The common complaints observed in group I patients include – joint pains (41%), fever (27%), weakness (24%), weight loss (22%), joint swelling (22%), rashes (14%), and hair loss (8%). The study conducted by various researchers reveal that the clinical manifestations experienced by the patients with autoimmune disease are disease specific. The study conducted by other researchers reveals that fatigue, fever, arthralgias, malaise, headache or weight loss are the common symptoms associated with SLE.[43] One study conducted by other researchers demonstrate that joint pains, morning stiffness, joint swelling are the common symptoms associated with RA.[32]

The common complaints observed in group II patients include – fever (93%), SOB (57%), myalgia (43%), headache (33%), loss of smell (17%), dry cough (13%), and nausea (7%). The studies conducted by various researchers demonstrated that dry cough, fever, fatigue, SOB are the common manifestations associated with COVID-19 (33-35).

The IgG and IgM levels are found to be higher in autoimmune diseases when compared with that of non-autoimmune diseases (infections) with a P value of less than 0.0001. The study conducted in 2016 by researchers stated that autoreactive IgG and IgM levels are most commonly elevated in autoimmune diseases such as SLE, and RA. Another study on COVID-19 patients demonstrate that IgG levels peak after 17-19 days of symptom onset whereas, IgM peaks approximately after 20-22 days of symptom onset.

In this study, the CRP levels are found to be significantly higher in group II patients when compared with group I patients. One study conducted in 2020 on COVID-19 patients suggest that CRP act as one of the strongest predictors of severe inflammation and respiratory failure. The study conducted in 2019 on the role of CRP in autoimmune diseases stated that CRP act as potential biomarker of inflammation but low levels of CRP are observed in SLE despite tissue inflammation and disease exacerbations.

In this study, the statistically significant difference in the levels of ESR was not observed between group I and group II patients. The mean of the ESR levels is found to be equivalent in both autoimmune diseases and severe COVID patients. The study conducted in 2020 on COVID patients suggest that ESR is positively associated with severity of COVID-19. The study conducted by other researchers on autoimmune diseases stated that CRP and ESR are not the specific markers of inflammation for the diagnosis of autoimmune diseases. The levels of ESR increases in most of the patients with autoimmune diseases whereas, in some patients, the

levels of ESR may be normal even if there is serious inflammation noted in that patient.

It is noted that IgG increases as the disease progresses in both group I and group II patients whereas, there is no significant difference observed in IgM levels of group I patients. Conversely, IgM levels increases as the disease progresses in group II patients. One study conducted on COVID patients in 2020 for the detection of antibodies post infection suggest that antibody tests might have an important role in detecting previous SARS-COV-2 infection. The study conducted by other researchers on antibodies in autoimmune diseases suggest that antibodies are directly related to the severity of the disease. Another study on autoimmune diseases demonstrates that due to the presence of low levels of IgM natural antibodies, the autoreactive IgG antibodies increases.

In this study, the drugs which are commonly prescribed for the group I (autoimmune diseases) patients include – Hydroxychloroquine (78%), prednisolone (49%), methotrexate (30%), azathioprine (11%), methyl prednisolone (11%), sulfasalazine (11%), mycophenolate mofetil (5%). The study conducted by other researchers on the drugs which are used commonly for the autoimmune condition states that hydroxychloroquine is the potential drug for the management of systemic autoimmune diseases such as SLE, RA, Sjogren's syndrome despite that it causes severe retinal toxicity even at low dose frequencies. Corticosteroids play an important role in inducing remission and management of autoimmune diseases. Methotrexate and sulfasalazine are most commonly used in the treatment of RA. Azathioprine is used in the management of MCTD (Mixed connective tissue disorders). Mycophenolate mofetil is gaining importance in recent times in the management of SLE patients.

The drugs which are commonly prescribed for the treatment of group II patients (severe COVID-19) in this study are as follows – Methyl prednisolone (77%), remdesivir (70%), dexamethasone (30%), tocilizumab (20%), prednisolone (2%). The study conducted on the use of corticosteroids in COVID patients suggest that corticosteroids may have a beneficial effect in reducing short term mortality and severity in COVID patients.

In another study conducted on the use of remdesivir in COVID patients states that this drug does not prove to provide beneficial effect in severely affected patients despite its wide use. There is not much evidence regarding the use of monoclonal antibodies such as tocilizumab in COVID patients, but it is now prescribed in severely ill patients.

5. CONCLUSION
In view of analysed data, we observed that Autoimmune diseases are more common in females whereas, severe COVID-19 infection is more common in males. RA is

the most common autoimmune diseases noted in our study population, followed by SLE and MCTD. The common complaints observed in patients with autoimmune diseases include joint pains, fever, weakness, weight loss, and joint swelling whereas, the complaints experienced by the patients diagnosed with severe coronavirus disease include fever, SOB, myalgia, headache, loss of smell, dry cough, and nausea. It is also observed that IgG and IgM levels are elevated in autoimmune disease when compared with severe COVID-19. The CRP was higher in patients with severe coronavirus disease whereas, ESR was found to be equivalent in both autoimmune disease and severe coronavirus disease. This study shows that increase in the immunoglobulin levels i.e., IgG and IgM are observed with the progression of disease in both autoimmune disease and coronavirus disease. The most common medications which are prescribed in autoimmune diseases include Hydroxychloroquine, prednisolone, and methotrexate whereas, the most common medication prescribed to patients with severe COVID-19 include Methyl prednisolone and remdesivir.

Hence, we conclude that autoimmune diseases are more prevalent in women of child-bearing age. IgG and IgM levels were found to be increased with increase in severity in both autoimmune disease and coronavirus disease. Hence, IgG and IgM antibody test may be useful as effective predictors in diagnosis and severity of autoimmune disease and severe coronavirus disease.

REFERENCES
1. NIH/US National Library of Medicine. Medline Plus Medical Encyclopedia Web site. Autoimmune disorders. Available at: https://medlineplus.gov/ency/article/ 000816.htm. Accessed March 2, 2018.
2. Fairweather D, Rose NR. Women and autoimmune diseases. Emerg Infect Dis., 2004; 10(11): 2005–11. Moulds, J. M. Introduction to antibodies and complement. Transfusion and Apheresis Science, 2009; 40(3): 185–188.
3. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. J Autoimmun, 2014; 48–49: 10–3.
4. Walsh SJ, Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. Am J Public Health, 2000; 90: 1463–6.
5. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmun Rev., 2010; 9: A387–94.
6. Kurahara D, Tokuda A, Grandinetti A, et al. Ethnic differences in risk for pediatric rheumatic illness in a culturally diverse population. J Rheumatol, 2002; 29: 379–83.
7. Schettino EW, Ichiyoshi Y, Casali P. Structure–function relation in natural and disease-associated human autoantibodies. In: Zanetti M and Capra JD, editors. The antibodies. Newark: Harwood Academic Publishers, 1996; 2: 155–203.
8. Kasaian MT, Casali P. Autoimmunity-prone B-1 (CD5 B) cells, natural antibodies and self recognition. Autoimmunity, 1993; 15: 315–329.
9. Casali P, Burastero SE, Nakamura M, Inghirami G, Notkins AL. Human lymphocytes making rheumatoid factor and antibody to ssDNA belong to Leu-1 þ B-cell subset. Science, 1987; 236: 77–81
10. Mohan C, Morel L, Yang P, Wakeland EK. Accumulation of splenic B1a cells with potent antigen-presenting capability Molecular mechanisms of autoimmunity 131 Autoimmunity Downloaded from informahealthcare.com by Universitaets- und Landesbibliothek Duesseldorf on 12/02/13 For personal use only. in NZM2410 lupus-prone mice. Arthritis Rheum, 1998; 41: 1652–1662.
11. Schettino EW, Ichiyoshi Y, Casali P. Structure–function relation in natural and disease-associated human autoantibodies. In: Zanetti M and Capra JD, editors. The antibodies. Newark : Harwood Academic Publishers, 1996; 2: 155–203.
12. Wu JF, Yang YH, Wang LC, Lee JH, Shen EY, Chiang BL Antinucleosome antibodies correlate with the disease severity in children with systemic lupus erythematosus. J Autoimmun, 2006; 27: 119–124.
13. Hylkema MN, van Bruggen MC, ten Hove T, de Jong J, Swaak AJ, Berden JH, Smeenk RJ Histone-containing immune complexes are to a large extent responsible for anti-dsDNA reactivity in the Farr assay of active SLE patients. J Autoimmun, 2000; 14: 159–168.
14. Galeazzi M, Morozzi G, Piccini M, Chen J, Bellisai F, Fineschi S, Marcolongo R. Dosage and characterization of circulating DNA: present usage and possible applications in systemic autoimmune disorders. Autoimmun Rev., 2003; 2: 50–55.
15. Witte, T. *IgM Antibodies Against dsDNA in SLE. Clinical Reviews in Allergy & Immunology,* 2007; *34(3): 345–347.*

16. Hahn BH Antibodies to DNA. N Engl J Med., 1998; 338: 1359–1368.

17. Adib M, Ragimbeau J, Avrameas S, Ternynck T. IgG autoantibody activity in normal mouse serum is controlled by IgM. J Immunol, 1990; 145(11): 3807–13.

18. Berneman A, Ternynck T, Avrameas S. Natural mouse IgG reacts with self antigens including molecules involved in the immune response. Eur J Immunol, 1992; 22(3): 625–33. doi:10.1002/eji.1830220303

19. Vargas ME, Watanabe J, Singh SJ, Robinson WH, Barres BA. Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. Proc Natl Acad Sci U S A, 2010; 107(26): 11993–8. doi:10.1073/pnas.1001948107

20. Hurez V, Kaveri S, Kazatchkine MD. Expression and control of the natural autoreactive IgG repertoire in normal human serum. Eur J Immunol, 1993; 23(4): 783–9. doi:10.1002/eji.1830230402

21. Abdou NI, Wall H, Lindsley HB, Halsey JF, Suzuki T. Network theory in autoimmunity. in vitro suppression of serum anti-DNA antibody binding to DNA by anti-idiotypic antibody in systemic lupus erythematosus. J Clin Invest, 1981; 67(5): 1297–304. doi:10.1172/JCI110158

22. Leandro MJ, de la Torre I. Translational mini-review series on B cell-directed therapies: the pathogenic role of B cells in autoantibody-associated autoimmune diseases—lessons from B cell-depletion therapy. Clin Exp Immunol, 2009; 157: 191–7.

23. Ooi JD, Holdsworth SR, Kitching AR. Advances in the pathogenesis of Goodpasture's disease: from epitopes to autoantibodies to effector T cells. J Autoimmun, 2008; 31: 295–300.

24. Singh RR. SLE: translating lessons from model systems to human disease. Trends Immunol, 2005; 26: 572–9.

25. Dong X, Cao YY, Lu XX, et al. Eleven Faces of Coronavirus Disease 2019. Allergy. 2020.

26. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 2020.

27. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print February 19, 2020]. Allergy. 2020. https://doi.org/10.1111/all. 14238.

28. Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med., May, 1994; 96(5): 457-62.

29. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol, Aug, 2014; 35(3): 347-69.

30. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. Intervirology, Dec 9, 2020: 1-12.

31. Sardu C, Cocco E, Mereu A, Massa R, Cuccu A, Marrosu MG, Contu P. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PLoS One., 2012; 7(3): e32487.

32. Bellamy N, Sothern RB, Campbell J, Buchanan WW. Circadian rhythm in pain, stiffness, and manual dexterity in rheumatoid arthritis: relation between discomfort and disability. Ann Rheum Dis 1991;50:243–8

33. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020; 395(10223): 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

34. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci., 2020; 63(3): 364-374. https://doi.org/10.1007/ s11427-020-1643-8

35. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print February 19, 2020]. Allergy. 2020. https://doi.org/10.1111/all. 14238.