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From Editors

Dear Esteemed Readers,
It is with great pride and enthusiasm that we present to you Volume 2, Issue 4 of the Journal of European Internal Medicine Professionals (JEIMP). As we continue our journey of advancing knowledge in the field of internal medicine, we are once again reminded of the pivotal role that high-quality research plays in shaping the future of medical practice.

This issue features a diverse collection of original research, reviews, and case studies that cover a broad spectrum of contemporary medical challenges. From the evolving understanding of humoral responses in hemodialysis patients post-COVID-19 vaccination to the assessment of motor development in individuals with special needs, each contribution brings valuable insights to the forefront of internal medicine.

Our featured articles offer a comprehensive analysis of clinical and histopathological predictors in IgA nephropathy, which is crucial for advancing our knowledge on renal survival in patients with nephrotic range proteinuria. In addition, studies on serum albumin levels and their impact on FDG uptake during gastrointestinal cancer staging present new perspectives that will undoubtedly inspire further research and clinical applications.

The review section in this issue addresses targeted treatment strategies for rheumatic diseases, particularly during pregnancy and lactation—a critical area that affects many patients globally. Additionally, a thought-provoking letter to the editor sheds light on 17q12 deletion syndrome, contributing to the growing body of knowledge on rare genetic conditions.

As we look ahead, our goal remains steadfast: to create a collaborative and informed community of internal medicine professionals. We are deeply grateful to our authors for their rigorous research, our reviewers for their insightful feedback, and our readers for their continued engagement with the journal.

We invite you to explore the rich content of this issue and consider how these findings can enhance your clinical practice or inspire future research. Your contributions and feedback are essential as we continue to build a platform that fosters innovation and excellence in internal medicine.

With warm regards and best wishes,

Assoc. Prof. Dr. Mehmet Emin Demir
Editor-in-Chief

Assoc. Prof. Dr Ercan Turkmen
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Original Article

Humoral Response Decreases in Hemodialysis Patients 6 Months After The Third Dose of COVID-19 Vaccine

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Abstract

Background: This study evaluated the antibody levels six months after administering the third dose of the COVID-19 vaccine in hemodialysis patients.

Methods: A total of 52 hemodialysis patients were enrolled in the study. Antibody levels were assessed using the Abbott SARS-CoV-2 immunoassay, designed to detect IgG antibodies targeting the receptor-binding domain of the S1 subunit of the SARS-CoV-2 spike protein.

Results: The incidence of COVID-19 infection within six months following the third vaccine dose was 29.6% (8 patients: 2 males, 25%; 6 females, 75%). Among patients who did not contract COVID-19 within this period, 9 were male (47.4%) and 10 were female (52.6%). There was no statistically significant association between gender and the incidence of COVID-19 within six months post-vaccination (p= 0.280). The median antibody level post-third dose was 7332.4 AU/mL (range: 10.5–40,000), which significantly decreased at the sixth month to 3238.4 AU/mL (range: 17–29,994.7) (p= 0.001). No significant difference between male and female patients was observed in the sixth-month antibody titers (p= 0.744). Furthermore, when analyzed by vaccine type, there was no statistically significant difference in the decline of SARS-CoV-2 IgG antibody levels between recipients of CoronaVac/Sinovac and BNT162b2 (Pfizer/BioNTech) [median (min-max) antibody levels: CoronaVac/Sinovac 2398.2 AU/mL (59.2–38,981.5); BNT162b2 (Pfizer/BioNTech) 11,325.7 AU/mL (17–40,000), (p= 0.181)] at the end of the sixth month.

Conclusion: Antibody titers in hemodialysis patients significantly decreased by the end of the sixth month following the third dose of the SARS-CoV-2 vaccine, independent of the vaccine type. This decline highlights the potential necessity for additional booster doses to enhance and maintain immune protection against SARS-CoV-2 in this vulnerable population.

Keywords: Hemodialysis, COVID-19 vaccine, SARS-CoV-2 antibody

INTRODUCTION

COVID-19, declared a pandemic by the World Health Organization (WHO) on March 11, 2020, is defined as a life-threatening viral epidemic that has significantly impacted human health (1). Since its onset in December 2019, the virus has spread globally, resulting in over 329 million confirmed cases and more than 5.5 million deaths to date (2). Hemodialysis patients represent a vulnerable population to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated morbidity and mortality, facing a 2- to 4-fold increased risk of death compared to the general population (3,4). While vaccination remains the most proven method to reduce the spread of the COVID-19 pandemic, maintaining long-term vaccine efficacy is crucial for combating newly emerging variants.

A recent meta-analysis reported that COVID-19 mRNA vaccines are highly effective, especially after second dose administration, against post-vaccination laboratory-confirmed SARS-CoV-2 infection, symptomatic COVID-19 infection, hospitalization, and mortality (5). Hemodialysis patients have a higher risk of COVID-19 infection due to increased comorbidities, suppressed

immune systems, and having to be in crowded hemodialysis rooms two/three days a week (6). It is also a known fact that 28 days after two doses of mRNA vaccine, dialysis patients and transplant recipients have lower seroconversion rates compared to controls (7-9).

Since no effective drug has been found to treat COVID-19, measures such as increasing decontamination by promoting personal hygiene and cleaning, maintaining social distancing, quarantine, and isolation, as well as increasing the number of immune people by expanding vaccination is very important to stop the spread of infection (6). Recent studies have shown that mRNA vaccines protect healthy individuals against emerging SARS-CoV-2 variants by inducing long-term immunological memory (10,11). However, especially in elderly and immunocompromised patients, antibody levels decrease rapidly within 6 months (12). These findings highlight the value of long-term monitoring of high-risk, renal disease patients to determine whether more booster vaccinations or different vaccination approaches are required.

This study examined SARS-CoV-2 IgG antibody titers against the S1 subunit of the spike protein as a marker of the humoral response to the 3rd dose BNT162b2 (Pfizer-BioNTech) or CoronaVac (Sinovac Life Sciences) vaccines in maintenance hemodialysis patients, six months after the third COVID-19 vaccination and aimed to compare the response in antibody titers and to investigate the frequency of SARS-CoV-2 infection after vaccination.

METHODS

Study Population

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Samsun University Clinical Research Ethics Committee, under protocol number 2022/3/8. Patients with hematological diseases, malignancies, connective tissue diseases, immunosuppressive therapy, a history of kidney transplantation, liver cirrhosis, chronic obstructive pulmonary disease, or congestive heart failure were excluded from the study.

The study included 52 adult hemodialysis patients (aged ≥18 years) who received a third dose of the COVID-19 vaccine between March 2021 and November 2022. All participants had been enrolled in a maintenance hemodialysis program for at least six months, and their antibody titers were eligible for measurement. Of these 52 patients, only 27 had measurable antibody levels at the end of the sixth month post-vaccination and were therefore included in the analysis.

Sociodemographic data, history of SARS-CoV-2 infection, COVID-19 vaccination status (including the number, dates, and types of vaccines received), and any COVID-19-related deaths were obtained from clinical file records. The hospital's electronic medical record system was utilized to access reverse transcriptase polymerase chain reaction (rRT-PCR) results and relevant laboratory data from routine follow-ups. All participants provided written informed consent for their involvement in the study.

Sample Collection and Analysis:

Venous blood samples were collected from participants on the 28th day following the third dose of either the CoronaVac or BNT162b2 vaccine, with a second sample collected at the end of the sixth month. Shortly after collection, the samples were centrifuged and stored at −20°C until analysis.

The Abbott "Alinity I" platform was used in accordance with the manufacturer's instructions for the quantitative analysis of antibodies using the SARS-CoV-2 IgG II Quant assay, an automated, two-step immunoassay designed for the detection of IgG antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. In this assay, paramagnetic microparticles coated with SARS-CoV-2 antigen bind to IgG antibodies specific to the spike protein in serum or plasma samples, reflecting the amount of spike protein-specific IgG present. The resulting chemiluminescence, measured in relative light units (RLU), is compared to the IgG II calibrator or standard to determine antibody levels.

A result of ≥50 AU/ml is considered positive. The analytical measurement range for this assay is 21–40,000 AU/ml, extendable to 80,000 AU/ml with a 1:2 dilution. The test has demonstrated high predictive accuracy, with a positive percent agreement of 99.4% (95% confidence interval [CI]: 96.50%–99.97%) and a negative percent agreement of 99.6% (95% CI: 99.15%–99.37%). It also showed agreement with a neutralization assay, with a positive percent agreement of 100.0% (95% CI: 95.72%–100.00%) (13).

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 21.0.0.1 for Windows (IBM SPSS). Data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or as median with minimum and maximum values, depending on the data distribution. Categorical variables were expressed as percentages. The Student's t-test or Mann-Whitney U test was used to compare differences in laboratory parameters between independent groups, based on the distribution of the data. Categorical variables were compared using the Chi-square test or Fisher's Exact test, as appropriate. Pearson correlation analysis was employed to examine correlations. The Wilcoxon test was used to assess differences between two dependent groups. A p-value of

Table 1. Socio-demographic characteristics and laboratory parameters of 27 patients participating in the study

Variable	Mean ± SD (range)/ median (min/max)
Age; year	59.7±10.3
Gender (Femal/Male); n and (%)	16/11 (59.3/40.7)
Dialysis time; months	32 (18/30)
Urea; mg/dL	123.26 ± 36.02
Creatinine; mg/dL	7.4 ± 1.9
Albumin; g/dL	3.58 ± 0.32
Alanine aminotransferase; U/L	15 (8 – 49)
Sodium; mmol/L	137.5 ± 3.45
Potassium; mmol/L	5.08 ± 0.69
Calcium; mg/dL	8.5 ± 0.63
Phosphorus; mg/dL	4.9 ± 1.24
Hemoglobin; g/dL	10.6 ± 1.16
White blood cell; 10^6/L	6260 ± 1639
Platelet; 10^6/L	194.78 ± 53.7
Ferritin; ng/mL	340 (118 – 805)

<0.05 was considered statistically significant.

RESULTS

Of the 52 patients undergoing hemodialysis in our clinic, who received the third dose of the COVID-19 vaccine (BNT162b2 vaccine or CoronaVac), only 27 patients whose antibody levels could be measured at the end of the 6th month were included in the study [11 male 40.7%, 16 female 59.3%; mean age 59.7±10.3 years (min 37, max 80); hemodialysis duration 32 months (min18, max 30)]. Laboratory values of the patients are listed in **Table 1**.

Antibody titers were lower in patients who had Covid within 6 months despite vaccination (12112.8 ± 6154.2) and in patients who did not have Covid (15172.5 ± 3851.5) (p= 0.004). In addition, antibody levels at the end of the sixth month were positively correlated with antibody levels at the end of the third dose (r= 0.58, p= 0.002). Among those who did not have COVID-19 within 6 months following the 3rd dose of vaccine, 9 of them were male, 47.4%, and 10 of them were female, 52.6%. There was no statistically significant difference between gender and the rate of COVID-19 infection within 6 months following the 3rd dose of vaccine (p= 0.280). Among those who did not have COVID-19 within 6 months following the 3rd dose of vaccine, 9 of them were male, 47.4%, and 10 of them were female, 52.6%. There was no statistically significant difference between gender and the rate of contracting COVID-19 within 6 months following the 3rd dose of vaccine (p= 0.280).

The last 3rd dose of vaccine administered in 9 patients was Biontech, and Sinovac in 18 patients. It determined that the last vaccine type of 8 patients who had COVID-19 within 6 months following the 3rd dose of vaccine was CoronaVac/Sinovac vaccine in 5 of them and BNT162b2 (Pfizer/Biontec) vacci-ne in 3. There was no statistically significant difference in the rate of contracting Covid within 6 months following the 3rd dose of vaccine, depending on the last vaccine type (p= 0.766). Excluding those who had COVID-19 in the last 6 months (n= 19), while the antibody level after the 3rd dose of vaccine was 7332.4 AU/mL (median) (min/max) (10.5-40000), a serious decrease was observed in the 6th-month antibody titer to 3238.4 AU/mL (median) (min/max) (17- 29994.7) (p= 0.001) (**Table 2**). When 8 patients who had Covid were excluded and the effect of gender on the 6th-month antibody titer was examined, the median 6th-month antibody titers was 3558.4 (408.8- 29994.7) in female patients (n= 10), while it was 1815.9 (17- 29262.2) in male patients (n= 9). There was no difference in 6th-month antibody levels between genders (p= 0.744). When the same analysis was performed according to the last vaccine type, no statistical difference was found between the decrease in SARS-CoV-2 IgG antibody level for both CoronaVac/Sinovac and BNT162b2 (Pfizer/Biontec) at the end of the 6th month [median (min-max) respectively; (CoronaVac/Sinovac; BNT162b2 (Pfizer/Biontec)] [2398.2 AU/mL (59.2 – 38981.5); 11325.7 (17 – 40000), (p = 0.181)] (**Table 3**).

DISCUSSION

This study demonstrated a significant decrease in anti-SARS-CoV-2 antibodies 6 months after the third dose of both CoronaVac/Sinovac and BNT162b2 (Pfizer/

Table 2. Antibody levels after the 3rd dose of vaccine and after 6 months, excluding those who had COVID-19 in the last 6 months

	Antibody Levels; N= 19, median (min-max)
After 3rd dose of vaccine antibody levels SARS-CoV-2 IgG Antibody titers (AU/mL)	7332.4 (10.5-40000)
After 6 months SARS-CoV-2 IgG Antibody titers (AU/mL)	3238.4 (17-29994.7)
P value	0.001

Table 3. SARS-CoV-2 IgG antibody level for CoronaVac/Sinovac and BNT162b2 (Pfizer/Biontec) at the end of the 6th month.

	BNT162b2(Pfizer/Biontec) (n=16) (min-max)	CoronaVac/Sinovac (n= 36) (min-max)	p value
End of the 6th month SARS-CoV-2 IgG Antibody titers (AU/mL) median (min-max)	11325.7 (17 – 40000)	2398.2 AU/mL (59.2 – 38981.5	0.181

Biontec mRNA vaccines) against SARS-CoV-2 in hemodialysis patients. Our findings were consistent with recently published studies describing decre-ased anti-SARS-CoV-2 antibodies over time in dialysis patients (14-16). The decrease in antibody levels was similar in both genders. Despite the third dose of vaccine, SARS-CoV-2 infection was obser-ved in approximately one-third of the patients (29.6%), but there was no deaths due to SARS-CoV-2 infection.

Patients with end-stage renal disease have been highly affected by the pandemic in terms of COVID-19 infection and complications due to having multiple comorbid conditions and a suppressed immune system, and the mortality rate is significantly high in those hospitalized (17). The frequency of SARS-CoV-2 infection in hemodialysis patients and mortality rates due to SARS-CoV-2 infection are significantly reduced in vaccinated individuals, and the administration of additional vaccine doses is important in increasing and maintaining protection against SARS-CoV-2 infection (18). In this study, even though one-third of the patients developed SARS-CoV-2 infection even after the third dose of vaccination, there was no deaths due to infection, which once again reveals the importance of vaccination.

After many vaccinations, neutralizing antibody levels decrease at a certain rate each year (19). As is known, antibody levels after naturally acquired SARS-CoV-2 infection decrease more slowly after 8 to 10 months than after vaccination (20,21). In our study, we observed a significant and rapid decrease in humoral response in hemodialysis patients in the 6th month after vaccination. This decrease was valid indiscriminately for both the CoronaVac/Sinovac vaccine and the BNT162b2 (Pfizer/Biontec) vaccine. Our findings supported other studies in the literature (12,16).

In a study conducted with healthcare workers, it was stated that the the incidence of symptomatic infec-tion with SARS-CoV-2 increased due to the rapid decline in antibody levels despite high vaccination rates, antibody levels after the second dose were higher in women than in men, antibody levels decrea-sed with age and antibody titers were lower in the group with immunosuppression (12). The fact that approximately one-third of the patients in our study were re-infected with SARS-CoV-2 within six months despite the third dose of vaccine can be explained by the fact that hemodialysis patients have a suppressed immune system compared to the healthy population, as stated in previous studies (12). Addi-tionally, the decrease in antibody levels observed over time in our study was independent of gender and age. This may be due to the small number of patients participating in the study, the high average age, and the low number of young patients.

In SARS-CoV-2 infection, neutralizing antibodies are associated with disease protection (22,23). In our study, neutralization tests could not be measured because they were complex and time-consuming, but antibody levels could be measured. The fact that the antibody titers of patients who had COVID-19 were lower than those of patients who had not COVID-19 within 6 months despite the vaccine reveals that the increase in the antibody level may protect against the disease.

Limitations of our study include limited follow-up to 6 months, single-center study, small sample size, lack of a control group, and lack of cellular immunity data. Hemodialysis patients often have comorbidi-ties and use many medications. The relationship between antibody titers and comorbidities and drug use could not be explained in the article.

CONCLUSION

Antibody titers in hemodialysis patients decline significantly six months after receiving both the CoronaVac (Sinovac) and BNT162b2 (Pfizer/BioNTech) mRNA vaccines. While SARS-CoV-2 infections may occur following the third vaccination, none of the infected patients in this study experienced mortality. In light of the emergence of new infection waves driven by viral mutations during the pandemic, it is evident that a fourth booster dose is necessary to maintain a protective humoral response in this vulnerable population. Additionally, strategies to prolong host immunity should be explored to ensure adequate protection for this patient group against SARS-CoV-2 and its variants.

DECLARATIONS

Ethics Committee Aproval: The study was initiated with the approval of the Samsun University Clinical Trial Ethics Committee (Date: 2022, Decision No:3/8).
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Original Article

Assessment of Individuals with Special Needs in Motor Development Presenting to the Pediatric Disability Health Board

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Abstract

Background: Developmental assessments are crucial for identifying moderate and severe special needs in children, ensuring their needs are recognized early and supported through Special Needs Reports for Children (SNRFC). This study aimed to evaluate the characteristics of pediatric patients with special needs in motor development who applied to the disability health board, focusing on their age, diagnoses, and the most common associated or accompanying disorders and the relationship between these terms.

Methods: A retrospective analysis was conducted on patients evaluated at the Pediatric Disability Health Board Polyclinic and the Physical Medicine and Rehabilitation Health Board Polyclinic.

Results: Among 1,507 patients admitted to the Pediatric Disability Health Board, 420 patients (6.57 ± 4.86 years) had varying levels of special needs related to motor development. Of these 420 patients, 147 patients (6.89 ± 4.74 years) were classified as having the most severe disability (HSCN), and 151 patients (5.19 ± 4.71 years) were categorized in the mildest disability group (HSN), with the remainder distributed across five intermediate levels in between. Cerebral palsy was the most frequent diagnosis in the HSCN. Other common diagnoses included epilepsy, specific motor developmental disorder, microcephaly, and hydrocephalus. Among the HSCN group, 60 individuals were also assessed as having severe disabilities in cognitive development. Trisomy 21 was the most common diagnosis, followed by specific motor developmental disorders and cerebral palsy in the HSN.

Discussion: The evaluation of individuals applying to the Pediatric Disability Health Board revealed that the largest group of patients in motor development had the HSN, followed by those with the HSCN. Cerebral palsy was the predominant diagnosis in the HSCN group, while trisomy 21 was most common in the HSN group. Additionally, patients with severe motor disabilities frequently had concurrent cognitive and nervous system impairments.

Conclusion: These findings provide valuable insights for physicians working in Pediatric and Physical Medicine and Rehabilitation Health Boards, facilitating more comprehensive evaluations of comorbid conditions and guiding the preparation of SNRFC for better patient management. Early recognition and documentation of special needs through these assessments play are critical in ensuring children receive timely developmental and educational support. This process helps address immediate and long-term needs, improving outcomes for children with disabilities.

Keywords: Health board, pediatric disability, motor development

INTRODUCTION

Disability is described as the inability to participate in regular daily activities and meet basic needs, as well as insufficient physical, mental, intellectual, and social capacities due to congenital or acquired diseases (1). Having a broader coverage, the term "having special needs" has started to supplant the word "disabled" in recent years. "Special need" refers to the requirement for educational, healthcare, rehabilitation services, assistive devices such as orthoses or prostheses, and environmental modifications. These needs, along with various social and economic rights and services, enable children with physical or functional differences from their typically developing peers to participate equally in

social life (2).

The early identification of motor disabilities and associated conditions is crucial for directing appropriate rehabilitation and therapeutic interventions. According to the World Health Organization (WHO), developmental disabilities, including motor disorders, impact nearly 200 million children globally, with the highest prevalence in low- and middle-income countries (1-3). Children with disabilities typically participate in fewer school, recreational, and social activities than their non-disabled peers, and as they become older, the diversity of their participation declines. Children with movement disorders represent a particularly vulnerable subgroup, as these disorders frequently affect not only motor function but also cognitive and sensory systems, which can lead to more complex care requirements (4,5).

Developmental assessments in pediatric populations are vital for the early detection and management of special needs, to help guide interventions, particularly for children with motor disabilities. Identifying such needs allows for the timely provision of appropriate interventions and services, improving overall outcomes and quality of life (3-6). In Turkiye, the Special Needs Report for Children (SNRFC) plays a central role in documenting these developmental challenges and ensuring access to resources. This report facilitates tailored support for children by categorizing their developmental challenges, including physical, cognitive, linguistic, and psychosocial needs (7,8).

As outlined in the SNRFC regulation, which took effect in February 2019, special needs levels are classified based on the severity of the condition. These levels include: “has special needs (HSN)” (20-39%), “mild special needs” (40-49%), “moderate special needs” (50-59%), “severe special needs” (60-69%), “very severe special needs” (70-79%), “significant special needs” (80-89%), and “has special condition needs (HSCN)” (90-99%). The classifications “very severe special needs,” “significant special needs” and “HSCN” all indicate a severe level of disability (9,10).

In the SNRFC framework, special needs are categorized into 23 distinct areas, encompassing physical structure, systems, functions, activities, life participation limitations, and diseases. Among these areas, movement development and rheumatology fall within the domain of physiatrists. According to current literature, movement development disorders rank as the second most common cause of disability in children, following psychiatric and cognitive conditions. This underscores the critical role of physiatrists in the SNRFC evaluation process, given their expertise in managing movement-related disabilities (9-12). Despite the critical importance of early developmental assessments in identifying and addressing the diverse needs of children with motor disabilities, there remains a paucity of comprehensive studies specifically examining the characteristics and comorbidities of pediatric patients seeking SNRFC (13).

In this study, a retrospective analysis for a detailed examination of the patients’ diagnoses and special needs levels, providing valuable insights into their developmental challenges was conducted on pediatric patients who applied for SNRFC at a major healthcare facility. This study focuses on evaluating the characteristics of pediatric patients with special needs in motor development who applied to the disability health board for a SNRFC assessment, focusing on their age, diagnoses, and the most common associated or accompanying disorders and the relationship between these terms. The findings of this research are expected to offer insights for clinicians and policymakers in pediatric healthcare and rehabilitation, promoting early and comprehensive care for children with motor disabilities.

METHODS

Participants

A retrospective analysis was conducted on patients evaluated at the Pediatric Disability Health Board Polyclinic and the Physical Medicine and Rehabilitation Health Board Polyclinic of Istanbul Kanuni Sultan Süleyman Training and Research Hospital between January 1, 2023, and December 31, 2023. Pediatric patients who applied for Special Needs Report for Children (SNRFC), aged 0-18 years that attended the Physical Medicine and Rehabilitation Outpatient Clinic were included. Applications related to age determination, status reports, and transfer procedures were excluded.

Data for this study were retrospectively extracted from the hospital’s electronic computing system, ensuring a comprehensive and accurate collection of patient records. Since all patient data were systematically documented within this digital platform, there were no missing data in the dataset, allowing for a complete analysis of the study population.

The results of the SNRFC assessments were analyzed in terms of sociodemographic characteristics, reasons for admission, and diagnoses related to the movement system, special needs levels, and areas of special needs.

Disability Assessment

The reports included in this study were based on evaluations conducted in accordance with the “Regulation on Special Needs Assessment for Children” published in the Official Gazette on 20.02.2019, issue number 30692 (7).

The assessment of movement development includes an evaluation made by an expert physiatrist through a comprehensive process involving a detailed review of the patient’s medical history, relevant imaging studies,

and a thorough physical examination. The findings from these assessments are meticulously documented in the patient's file and entered into the hospital's electronic computing system for accurate record-keeping and further analysis. The assessment of the movement development encompasses six specific categories. These categories include:

1. Gross motor development,
2. Fine motor development,
3. Amputations,
4. Fractures,
5. Congenital or acquired deformities of the locomotor system, infections, and other locomotor issues arising from diseases or treatments affecting the locomotor system,
6. Pain, which was assessed separately.

For gross and fine motor development, children are further categorized by developmental stages starting from birth to allow for a more detailed evaluation. In cases of amputations and fractures, the assessment accounts for both upper and lower extremities, as well as unilateral or bilateral involvement (7).

Ethical Approval

Ethics committee approval for this study was granted by the Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (approval no: KAEK/2024.09.190), in compliance with the Declaration of Helsinki. All patient data were anonymized to maintain confidentiality, ensuring that no identifiable information was used in the analysis. Since this was a retrospective study, formal consent from patients was waived, but all data were collected and handled following institutional guidelines to ensure ethical integrity.

As the study included the reports of all patients admitted between January 1, 2023, and December 31, 2023, the entire population was retrospectively incorporated into the analysis. Consequently, no additional sampling was performed, and the study was based solely on the existing study population (study group). Since the goal was to include the entire population, a sample eligibility test was deemed unnecessary.

STATISTICAL ANALYSIS

The data collected from all participants in the study group were analyzed using IBM SPSS (Version 21.0, Armonk, NY: IBM Corp.). Initially, a normality analysis was conducted, with the Kolmogorov-Smirnov test applied to assess the distribution of special needs levels and proposed special needs between boys and girls. To evaluate gender-based differences in the prevalence of motor disabilities, a chi-square test was applied. Descriptive statistics, including mean and standard deviation, were used to evaluate the data and presented in tables. Proportional data were shown as percentages (%), numerical data as counts (n), and normally distributed data as mean ± standard deviation. Statistical significance was set at $p<0.05$.

RESULTS

The data were determined to be normally distributed, allowing for the use of parametric statistical methods. Between January 1, 2023, and December 31, 2023, a total of 1,507 pediatric patients, with a mean age of 9.11 ± 2.53 years, applied to the Pediatric Disability Health Board seeking the Special Needs Report for Children (SNRFC). Among these patients, 48.2% (n=727) were first-time applicants, 18.4% (n=277) were appeal cases, and 33.4% (n=503) were renewals. The majority of the patients, 93.6% (n=1,412), were diagnosed with at least one condition falling under a special needs category.

Motor Development-Related Special Needs

Out of the total 1,507 patients, 420 (27.8%) were identified as having varying levels of special needs related to motor development, with a mean age of 6.57 ± 4.86 years. Among these 420 patients, 47.8% (n=201) were female, and 53.2% (n=219) were male. A statistically significant difference was found between the levels of special needs in boys and girls ($p<0.02$).

The classification of these 420 patients based on the severity of motor disabilities revealed that 35% (n=147) were categorized as having the most severe disability (HSCN), while 35.9% (n=151) were placed in the mildest disability group (HSN). The remaining patients were distributed across five intermediate disability levels. Results are presented in **Table 1.**

Table 1. Distribution of special needs among patients

Category	Motor Development Special Needs Patients (N=420)	Percentage
Gender Distribution		
Boys	201	47.8%
Girls	219	53.2%
Special Needs Classification		
HSCN (Most Severe)	147	35%
HSN (Mildest)	151	35.9%
Intermediate Disability Levels	122	29.1%

HSCN Group (Most Severe Disability)
The average age of the 147 patients classified as having the most severe disability (HSCN) was 6.89 ± 4.74 years. Cerebral palsy was the most common diagnosis in this group, affecting 57.8% of the patients. Other prevalent diagnoses included epilepsy (12.9%), specific motor developmental disorder (10.9%), microcephaly (6.8%), and hydrocephalus (6.1%).

A notable finding was that 40.8% (n=60) of the patients in the HSCN group also had severe cognitive developmental disabilities in addition to their motor impairments, highlighting the frequent overlap between motor and cognitive disabilities in this population.

HSN Group (Mildest Disability)
In the mildest disability group (HSN), consisting of 151 patients, the mean age was 5.19 ± 4.71 years. Trisomy 21 (Down syndrome) was the most common diagnosis in this group, accounting for 29.8% of cases. This was followed by specific motor developmental disorder (23.1%) and cerebral palsy (6.6%). The relatively high prevalence of developmental delays in children with trisomy 21 and other mild motor impairments underscores the need for early intervention and ongoing developmental support.

Overall Distribution of Diagnoses
Across the entire cohort of 420 patients who had a special need in motor developmental assessment, cerebral palsy was the most frequent diagnosis, followed by trisomy 21, specific motor developmental disorder, epilepsy, and microcephaly. The findings are shown in Table 2.

DISCUSSION

TThe results of this study highlight the diverse spectrum of motor development-related special needs among pediatric patients applying for the SNRFC assessment. Notably, 27.8% of the 1,507 patients exhibited varying levels of disability relevant to motor development, underscoring the importance of early and comprehensive assessments. Among these children, the distribution between the most severe and mildest disability groups (HSCN and HSN, respectively) reveals a wide range of motor impairments, with significant implications for clinical management and intervention strategies.

A key finding in this study is the significant gender difference in motor disabilities, with boys presenting a higher prevalence compared to girls. This aligns with existing literature suggesting that boys are more commonly affected by certain neurodevelopmental and motor disorders, such as cerebral palsy (9,12). Research into gender differences in motor developmental disabilities suggests that both biological and environmental factors play a crucial role in shaping these disparities (14).

Studies indicate that motor development may follow distinct patterns in boys and girls, with boys often exhibiting delayed motor milestones compared to girls (15). These differences have led to the recommendation of gender-specific norms for clinical assessments to ensure more accurate diagnoses and intervention plans. Additionally, the response to stimulating activities, such as physical therapy or play-based interventions, has been found to differ between genders, with boys and girls benefiting from tailored approaches that align with their developmental trajectories (16). This highlights the importance of individualized therapeutic strategies that account for gender-specific needs, ultimately improving the efficacy of early interventions (17).

In the most severe disability group (HSCN), cerebral palsy was the most common diagnosis, in consistence with global trends where cerebral palsy is recognized as the leading cause of physical disability in children (18). Additionally, many patients (%40.8) in the HSCN group exhibited comorbid cognitive disabilities, further complicating their developmental trajectory and necessitating a multidisciplinary approach to care. The high rate of comorbidity suggests that comprehensive evaluations of both motor and cognitive functions are essential to develop targeted interventions that address the full spectrum of impairments (1,6,8).

In contrast, the mildest disability group (HSN) was dominated by children with trisomy 21 (Down syndrome). While children with Down syndrome typically have mild to moderate motor impairments, early interventions can significantly enhance their motor development. The presence of the diagnosis of "specific motor developmental disorder" in both severe and mild disability groups highlights the complexity and variability in motor development, even within similar diagnostic categories. This finding also underscores the importance of individualized care plans that account for both the severity of the disability and the specific needs of the child (6,19,20).

Table 2. Diagnoses in different special needs groups of special needs among patients

Diagnosis	HSCN Group (n=147)	HSN Group (n=151)	Overall (n=420)
Cerebral Palsy	57.8 %	6.6 %	27.8 %
Trisomy 21	0.2 %	29.8 %	13.8 %
Specific Motor Development Disorder	10.9 %	23.1 %	17.2 %
Epilepsy	12.9 %	3.2 %	7.7 %
Others	18.2 %	37,3 %	33.5 %

HSN; Has Special Needs, HSCN; Has Special Condition Needs

The overall results emphasize the role of physiatrists and other specialists in the comprehensive assessment and management of disability relevant to motor development. With movement-related disorders being the second most common cause of pediatric disability after psychiatric and cognitive conditions, physiatrists play a critical role in evaluating and managing these patients. The significant overlap between motor and cognitive impairments, especially in severe cases, further highlights the necessity of a multidisciplinary approach that includes pediatricians, neurologists, and mental health professionals to ensure holistic care (3,6,21).

Developmental assessments in pediatric populations are crucial for the early detection and management of special needs, guiding targeted interventions, especially for children with motor disabilities. The findings of this study will help identify such needs, facilitating timely access to appropriate interventions and services, ultimately enhancing overall outcomes and quality of life for affected children. Early intervention has been well-documented to play a pivotal role in improving the long-term prognosis for children with conditions such as cerebral palsy, Down syndrome, and other motor developmental disorders. In the most severe cases, such as those classified under HSCN, initiating therapy, rehabilitation, and multidisciplinary support early in life can significantly enhance motor skills, cognitive function, and overall quality of life. For children with less severe disabilities, early interventions can potentially prevent the progression of secondary complications, such as musculoskeletal deformities, and foster greater independence in daily living (22,23).

This study's strengths lie in its comprehensive and inclusive approach, evaluating all patients who applied for the SNRFC assessment within the specified timeframe. As a retrospective cohort study, it provides valuable insights into the characteristics and distribution of disabilities in motor development without the introduction of selection bias typically associated with prospective studies.

Limitations

The retrospective nature of the study also presents certain limitations. The reliance on existing records may introduce inconsistencies or omissions in the data. Additionally, while the study benefits from a large sample size, it is constrained by its observational design, which limits the ability to establish causality or control for potential confounding variables. Despite these limitations, the study offers important insights into the prevalence and severity of disabilities in motor development, contributing to the understanding and management of pediatric special needs.

CONCLUSION

This study provides valuable insights into the characteristics of pediatric patients with disabilities relevant to motor development who applied for SNRFC assessments. The findings reveal a wide spectrum of motor impairments, with a significant portion of patients experiencing severe disabilities, often accompanied by cognitive impairments. The gender-based differences in motor disabilities call for gender-sensitive approaches to both assessment and treatment. Additionally, the high rate of comorbidities, especially in severe cases, underscores the importance of multidisciplinary care models. Future research should focus on developing a more comprehensive assessment scheme as well as the long-term effects of early interventions, personalized rehabilitation strategies, and the integration of social and cognitive support provided by these schemes to enhance patient outcomes.

DECLARATIONS

Conflict of interests: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

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Original Article

Clinical and Histopathological Predictors of Renal Survival in IgA Nephropathy Patients with Nephrotic Range Proteinuria: A Retrospective Survival Analysis

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Abstract

Background: IgA nephropathy (IgAN) presents with a wide spectrum of clinical features, most commonly hematuria accompanied by subnephrotic proteinuria. Nephrotic range proteinuria is rare, observed in approximately 6% of patients at diagnosis. Limited studies have examined the relationship between clinicopathological characteristics and renal prognosis in IgAN patients with nephrotic range proteinuria.

Methods: This retrospective, single-center case-control study included 114 patients diagnosed with IgAN via kidney biopsy at Şişli Hamidiye Etfal Training and Research Hospital from April 2004 to December 2016. Patients were divided into two groups: nephrotic (≥3.5 g/day) and subnephrotic (<3.5 g/day) proteinuria. Primary outcomes included a doubling of serum creatinine, while secondary outcomes measured the initiation of renal replacement therapy.

Results: Patients with nephrotic range proteinuria had significantly lower serum albumin levels (p=0.001), higher cholesterol levels (p=0.03), and increased fibrocellular crescent formation (p=0.01). Cox regression analysis identified baseline serum creatinine, uric acid, and albumin levels, along with histopathological findings such as glomerulosclerosis and crescent formation, as significant predictors of treatment response. The Kaplan-Meier analysis showed that patients with nephrotic range proteinuria had worse renal survival, with a significantly higher proportion reaching primary and secondary endpoints compared to the subnephrotic group.

Conclusion: Histopathological findings, particularly fibrocellular crescents, were more common in patients with nephrotic range proteinuria, and their presence was associated with poorer renal survival and lower treatment response rates. These patients require closer follow-up and may benefit from more aggressive therapeutic strategies.

Keywords: IgA nephropathy, proteinuria, nephrotic range, crescentic glomerulonephritis, renal survival, treatment outcome

INTRODUCTION

Immunoglobulin A nephropathy (IgAN), first described by Berger and Hinglais in 1968, is characterized by predominant glomerular mesangial deposition of IgA (1). While the "idiopathic" form of the disease is common, secondary forms associated with various diseases have also been described. Idiopathic IgAN remains the most frequent primary glomerulonephritis worldwide, accounting for up to 30-50% of cases in some Asian populations and around 20-30 % in Europe (2-4). In Turkey, IgAN is the most common primary glomerulonephritis, with a prevalence of 25.7 % (5).

Patients with IgAN present with a wide range of clinical manifestations, including episodic macroscopic hematuria (40-50%), asymptomatic hematuria with proteinuria (30-40%), and nephrotic range proteinuria and nephrotic syndrome about 6% of cases. Additionally, some patients present with acute kidney injury, particularly in older adults. The disease typically peaks in the second and third decades of life, with a male predominance. The long-term prognosis of IgAN varies, with up to 50% of patients progressing to end-stage renal disease (ESRD) within 20 years of diagnosis (6).

The pathogenesis of IgAN involves the accumulation of polymeric IgA1 molecules in the glomerular mesangium,

triggering mesangial cell proliferation and the release of extracellular matrix proteins and inflammatory mediators. Poorly galactosylated IgA1, particularly in its polymeric form, is thought to play a key role in disease progression. Genetic factors, as well as immune responses involving complement activation and cytokine release, further contribute to the development of glomerular damage (7). A recent report identified IgA autoantibodies targeting mesangial cells and specific autoantigens (β2-spectrin and CBX3) in both gddY mice and patients with IgA nephropathy (IgAN), redefining IgAN as a tissue-specific autoimmune disease potentially driven by commensal bacteria through molecular mimicry (8).

Histopathological findings in IgAN vary, ranging from mild mesangial proliferation to more severe forms such as crescentic glomerulonephritis. The presence of crescents, particularly fibrocellular crescents, has been associated with a more rapid progression to end-stage renal disease (ESRD). Treatment options for IgAN are primarily aimed at controlling proteinuria and blood pressure, with the use of renin-angiotensin system (RAS) inhibitors being the mainstay of therapy. In patients with persistent proteinuria despite optimal supportive care, corticosteroids and other immunosuppressive agents may be required (9). Moreover, new therapies are rapidly emerging that target various pathways, cells, and mediators involved in disease pathogenesis, including B cell priming in the gut mucosa, the cytokines APRIL and BAFF, plasma cells, complement activation, and the endothelin pathway.

Previous studies revealed the strong association between IgAN and proteinuria, as higher levels of proteinuria (≥1 g/day) are strongly associated with worse histological findings, including mesangial hypercellularity, segmental sclerosis, tubular atrophy, and the presence of crescents, which indicate more advanced kidney damage. Proteinuria is also one of the strongest clinical predictors of progression to kidney failure in patients with IgAN (10,11). The risk of kidney failure is particularly high in patients with baseline proteinuria levels ≥1.0 g/day, where even reductions in proteinuria to 0.3 to <0.5 g/day can not lower risk effectively. This demonstrates that patients starting with high proteinuria need more aggressive management to lower their risk of kidney failure, emphasizing the importance of achieving significant reductions in proteinuria (10,11).

This study aims to investigate the clinical and pathological features of IgAN patients presenting with nephrotic range proteinuria and to evaluate their response to treatment and long-term renal outcomes.

METHODS

Study Design and Population

This retrospective, single-center case-control study was conducted at the Şişli Hamidiye Etfal Training and Research Hospital, Nephrology Clinic. The study included 114 patients diagnosed with IgAN via kidney biopsy between April 2004 and December 2016. Patients were categorized into two groups based on proteinuria levels: nephrotic (≥3.5 g/day) and subnephrotic range (<3.5 g/day). A 1:3 matching case-control design was used, with patients matched by age, sex, and comorbidities (diabetes, hypertension).

Data Collection

Demographic, clinical, and laboratory data were extracted from patient records. Variables collected included age, gender, blood pressure, serum creatinine, serum albumin, uric acid, total cholesterol, 24-hour urinary protein excretion, and the presence of microscopic hematuria. Kidney biopsies were evaluated for glomerular sclerosis, crescent formation, mesangial hypercellularity, endocapillary proliferation, and tubulointerstitial damage. All kidney biopsies were examined by the same pathologist to ensure consistency in histological assessment.

Treatment Protocol

All patients received standard care, including dietary sodium restriction (2 g/day) and antihypertensive therapy aimed at achieving blood pressure targets of <130/80 mmHg for patients with proteinuria <1 g/day and <125/75 mmHg for those with ≥1 g/day. Patients with persistent proteinuria ≥1 g/day despite maximal RAS inhibition for six months were treated with corticosteroids, with some receiving intravenous pulse methylprednisolone followed by oral steroids. Patients unresponsive to corticosteroids received additional immunosuppressive therapy, such as mycophenolate mofetil.

In the treatment of IgAN, antihypertensive medications primarily included agents targeting the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are effective in reducing proteinuria and controlling blood pressure. Additional antihypertensive agents such as beta-blockers, calcium channel blockers, and diuretics were also utilized as adjunctive therapy when necessary. The antihypertensive therapy was administered with the aim of achieving a target blood pressure of <130/80 mmHg for patients with proteinuria <1 g/day, and <125/75 mmHg for those with proteinuria ≥1 g/day. The dosage and choice of antihypertensive medications were individualized based on each patient's clinical condition and disease progression. Therapy was optimized in accordance with current clinical guidelines, with regular follow-up ensuring appropriate dose adjustments to maintain optimal blood pressure control.

Outcome Measures

The primary outcome was a doubling of serum creatinine from baseline. The secondary outcome was

Table 1. Demographical and laboratory results of the participants

Parameter	Nephrotic Range Proteinuria Group (Mean ± SD)	Subnephrotic Range Proteinuria Group (Mean ± SD)
Age (years)	45 ± 15	44 ± 14
Male (%)	72%	67%
Follow-up (months)	35.7 ± 32.6	45.7 ± 38
Serum Creatinine (mg/dL)	1.8 ± 0.6	1.4 ± 0.5
Serum Albumin (g/dL)	3.0 ± 0.5	4.0 ± 0.4
Total Cholesterol (mg/dL)	250 ± 30	210 ± 25
Uric Acid (mg/dL)	7.0 ± 1.2	6.0 ± 1.0
Proteinuria (g/day)	4.0 ± 0.8	2.5 ± 0.7

the initiation of renal replacement therapy (dialysis or transplantation). Treatment response was classified as complete remission (proteinuria <0.3 g/day), partial remission (proteinuria <1 g/day or a 50% reduction), or non-response.

STATISTICAL ANALYSIS

The data were analyzed using IBM SPSS (Version 21.0, Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation. Comparisons between groups were made using the independent t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Kaplan-Meier survival analysis was used to estimate time to primary and secondary outcomes, and Cox regression analysis was performed to identify predictors of renal survival. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The study included 25 patients in the nephrotic range proteinuria group (Group 1) and 75 patients in the subnephrotic range proteinuria group (Group 2). The mean follow-up period was 35.7 ± 32.6 months in Group 1 and 45.71 ± 38 months in Group 2 (p=0.24). Serum albumin levels were significantly lower in Group 1 (p=0.001), while cholesterol levels were higher (p=0.03). The clinical and laboratory features of the participants are given in **Table 1.** The study was designed as a matched case control study, so for 25 nephrotic range proteinuria patients, 75 subnephrotic range proteinuria patients were selected. The selection was made in accordance with the demographic and clinical features of the group.

Table 2. Histopathological features of the study groups

Histopathological Feature	Nephrotic Range Proteinuria Group (%)	Subnephrotic Range Proteinuria Group (%)
Fibrocellular Crescents	46.2	14.2
Global	27.2	22.0
Tubulointerstitial Damage	40.0	33.3

Appropriate statistical methods, including sensitivity analyses, were applied to ensure that the missing data did not significantly impact the overall results.

Fibrocellular crescent formation was more prevalent in Group 1 (p=0.01), and the complete remission rate was significantly lower (p=0.004) compared to Group 2 (**Table 2**).

Renal Outcomes

Doubling serum creatinine occurred in 20% of patients in Group 1, compared to 4% in Group 2 (p=0.022). Kaplan-Meier analysis revealed that the time to primary outcome in Group 1 was significantly shorter with 87.3 months as opposed to Group 2, with 134.5 months (log-rank p<0.001) (**Figure 1**). The secondary outcome, renal replacement therapy or transplantation need was observed in 32% of patients in Group 1 and 5.3% in Group 2 (p=0.003) (**Figure 2 and Figure 3**).

Cox Regression Analysis

Cox regression analysis identified age (HR= 1.05 and p=0.002), baseline serum creatinine (HR= 1.65, p=0.005), uric acid (HR= 1.28, p=0.002), and albumin levels (HR= 0.88, p=0.001) as independent predictors of renal survival. Histopathological findings, including global glomerulosclerosis (HR= 1.45, p=0.003), crescent

Table 3. Cox regression analysis for renal survival

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-value
Age (years)	1.05	1.02-1.07	0.002
Baseline Serum Creatinine (mg/dL)	1.65	1.17-2.44	0.005
Serum Albumin (g/dL)	0.88	0.72-1.09	0.001
Uric Acid (mg/dL)	1.28	1.03-1.55	0.002
Global Glomerulosclerosis (%)	1.45	1.02-2.06	0.003
Total Crescents (%)	4.6	1.16-13.0	0.004
Tubulointerstitial Damage (%)	1.7	1.00-2.63	0.01

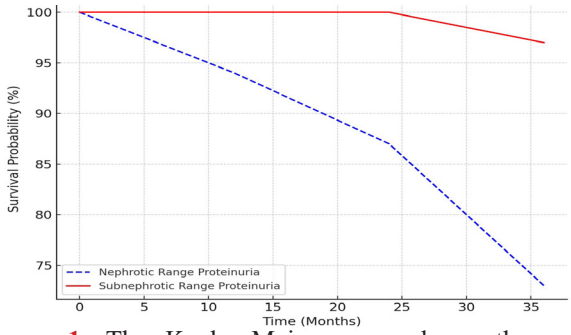

Figure 1. The Kaplan-Meier curve shows the survival probability for the primary outcome in patients with nephrotic and subnephrotic range proteinuria.

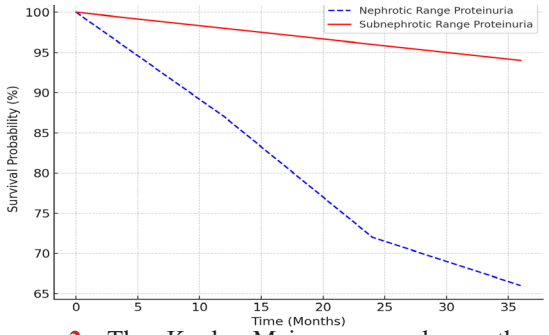

Figure 2. The Kaplan-Meier curve shows the survival probability for the secondary outcome in patients with nephrotic and subnephrotic range proteinuria.

formation (HR= 4.6, p=0.004), and tubulointerstitial damage (HR= 1.7, p=0.01), were also significant determinants (Table 3).

DISCUSSION

The present study aimed to investigate the clinical and pathological features of IgAN patients with nephrotic range proteinuria and assess their long-term renal outcomes. The key findings demonstrated that patients with nephrotic range proteinuria had significantly worse renal survival compared to those with subnephrotic proteinuria, as indicated by higher rates of serum creatinine doubling and progression to end-stage renal disease (ESRD). Histopathologically, fibrocellular crescent formation was more prevalent in patients with nephrotic range proteinuria, and this was associated with poorer treatment response and renal prognosis. Cox regression analysis identified baseline serum creatinine, uric acid levels, albumin, glomerulosclerosis, and crescent formation as significant predictors of renal survival. These results suggest that patients with nephrotic range proteinuria require closer monitoring and more aggressive therapeutic interventions to improve outcomes.

Immunoglobulin A (IgA) nephropathy is the most common glomerular disease worldwide, characterized by the deposition of polymeric IgA in the mesangium and sometimes the capillary mesangium (12). The proliferative and crescentic forms of IgAN are associated with nephrotic range proteinuria, accelerated hypertension, and faster progression to ESRD, although nephrotic range proteinuria is rare at presentation, occurring in approximately 6% of cases (13). Crescent formation varies in prevalence from 5-60%, with diffuse crescentic lesions (>50% involvement) observed in 1-4% of patients, making them rare but significant (14). While crescent formation was not highlighted as a predictor of renal survival in the Oxford classification or the VALIGA studies due to the low prevalence in those cohorts, several studies have since established that crescent formation negatively impacts prognosis. A meta-analysis by Xue Shao et al., reviewing 5285 IgAN patients, confirmed that those with crescents had

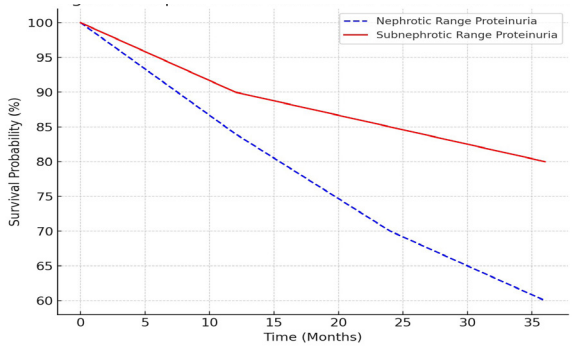

Figure 3. The Kaplan-Meier curve shows the renal survival probability in patients with nephrotic and subnephrotic range proteinuria.

lower GFR, higher proteinuria levels, and more frequent immunosuppressive therapy use, reinforcing crescent formation as a key prognostic factor in progression to renal failure (15).

Zhonghui Jia et al. further reported that, in a cohort of 63 IgAN patients with <50% crescent involvement, 14.2% had urinary protein levels above 3.5 grams, with crescents accounting for 5-47% of the lesions, most of which were cellular crescents (16). In our study, crescents were identified in 48% of patients with nephrotic range proteinuria, with a notable increase in fibrocellular crescents in this group, compared with subnephrotic proteinuria.

A study by Liang et al. involving 89 patients with IgAN, 19.1% of whom had nephrotic range proteinuria, reported a higher rate of crescent formation in those with nephrotic proteinuria. Of these, 91.8% had less than 25% crescent involvement (17). In this cohort, 13.3% patients experienced a 50% increase in serum creatinine or required dialysis after a median follow-up of 18 months, 28.6% of those with nephrotic proteinuria reaching these endpoints after a median follow-up of 11 months. Similarly, Silva et al. found that despite conventional treatment, 40% of IgAN patients with <50% crescent involvement had poor renal outcomes (18). In a retrospective study including 146 primary IgAN patients conducted by Walsh et al., the presence of any crescents (including fibrous crescents) was a significant independent predictor of doubling serum creatinine, ESRD, or death (19). Furthermore, a study by

Katafuchi et al. involving 702 patients demonstrated that crescents were associated with worse renal survival (20). In our study, 26% of patients with crescents progressed to ESRD, compared to 5.8% of those without crescents.

Proteinuria levels greater than 1 g/day are indicative of more severe IgAN, and uncontrolled proteinuria is a major risk factor for disease progression. The rate of progression is low when proteinuria is below 1 g/day but increases significantly when proteinuria exceeds 3-3.5 g/day. In a prospective cohort study of 332 patients, it was shown that the combined incidence of dialysis and death was significantly higher in patients with baseline proteinuria >1 g/day compared to those with lower levels (17% vs. 3% at 10 years, and 41% vs. 10% at 20 years). Patients who reduced their proteinuria to <1 g/day with treatment had lower rates of dialysis and death compared to those with persistent proteinuria above 1 g/day (21). However, a follow-up study of 542 patients by Reich et al. found that for patients with baseline proteinuria >3 g/day, the rate of renal function decline was 24 times faster, but there was no significant difference in progression to renal failure between those achieving partial remission (<1 g/day) and those starting with baseline proteinuria <1 g/day. In our study, doubling of serum creatinine and progression to ESRD were more frequent in patients with nephrotic range proteinuria. Even when partial remission was achieved, renal survival was worse in nephrotic group compared to subnephrotic group (22).

In a study by James Tumlin et al., even low levels of crescents were associated with poor outcomes and faster progression to ESRD. Notably, no correlation was found between nephrotic range proteinuria and treatment response or progression to ESRD in these patients (23). In our study, patients with nephrotic range proteinuria had significantly lower rates of complete remission and higher rates of treatment resistance. However, when assessing treatment response on renal survival, no significant difference was observed between the nephrotic and subnephrotic groups.

The use of corticosteroids and other immunosuppressive agents in the treatment of IgAN remains controversial. In patients with persistent proteinuria >1 g/day despite optimal supportive care, combining non-immunosuppressive therapy with immunosuppressive treatment is crucial (24). Some authors advocate for more aggressive treatment in patients with nephrotic proteinuria and/or rapidly progressive disease, especially if cellular crescents are present in more than 10% of glomeruli (25-26).

Higher serum uric acid levels, lower serum albumin and older age are associated with adverse outcomes (27-30). Similarly this study demonstrated that uric acid, and albumin have strong impact on IGAN-related outcomes.

In our study, although the treatment protocols for both groups were similar (with intravenous steroid use being more frequent in patients with nephrotic range proteinuria), the rate of treatment resistance was 9 times higher in the nephrotic group. We believe that the difference in crescent prevalence between the two groups may have contributed to the disparity in treatment response.

Limitations

This study has several limitations that need to be acknowledged. First, the retrospective design introduces inherent biases, such as reliance on medical records and the possibility of missing data, which could affect the accuracy of clinical and laboratory parameters. Moreover, being a single-center study, the findings may not be generalizable to other populations or healthcare settings, particularly those with different ethnic backgrounds or healthcare practices. Second, the sample size, especially in the nephrotic range proteinuria group, was relatively small. This limited the statistical power of certain analyses, such as subgroup comparisons and multivariate adjustments, which may have impacted the robustness of our conclusions. Third, the study did not account for genetic factors or differences in treatment regimens beyond corticosteroids and RAS blockers, which may have influenced disease progression and patient outcomes. The heterogeneity in immunosuppressive therapy could also have led to varying treatment responses that were not fully captured. Lastly, the follow-up period varied between patients, with some having relatively short observation times. This could have led to underestimation of long-term outcomes such as progression to ESRD, particularly for those who were followed for less than three years.

CONCLUSION

This study demonstrated the outcome differences between IgAN patients presenting with nephrotic and subnephrotic proteinuria and the possible factors interacting with this outcome. The patients with nephrotic range proteinuria had worse renal outcomes, including higher rates of treatment resistance and progression to ESRD, compared to those with subnephrotic proteinuria. Histopathological findings, particularly the presence of fibrocellular crescents, were significant predictors of poor renal survival and treatment outcomes.

Given these findings, it is clear that patients with nephrotic range proteinuria require closer monitoring and potentially more aggressive therapeutic approaches. Early identification of high-risk patients, including those with crescent formation, is critical for optimizing treatment and preventing long-term kidney damage. While the use of corticosteroids and immunosuppressive agents remains controversial, they may be necessary for patients with persistent proteinuria despite optimal supportive care.

Further research, particularly multicenter studies with larger cohorts and longer follow-up durations, is needed to better understand the optimal management strategies for these high-risk patients and to confirm the role of crescent formation as a prognostic marker in IgAN.

DECLARATIONS

Ethics approval and consent to participate: This study was produced from the graduation thesis of Feyza Bayraktar, MD., and was applied for approval by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital. Written informed consent is not available since it is retrospective. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: No specific funding was received for this study.

Authors' contributions: Dr. Feyza Bayrakdar Çağlayan designed the study, collected the data, and performed the data analysis. Dr. Taner Baştürk supervised the study and contributed to the interpretation of results. Dr. Abdulkadir Ünsal provided overall guidance and critical revisions. All authors read and approved the final manuscript.

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Original Article

Impact of Serum Albumin Levels on FDG Uptake in the Liver, Spleen, and Bone Marrow During Gastrointestinal Cancer Staging: A PET-CT Study

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Abstract

Background: Serum albumin is an essential biomarker in cancer patients, reflecting nutritional status and systemic inflammation. This study investigates the impact of serum albumin levels on FDG uptake in the liver, spleen, and bone marrow during the staging of gastrointestinal cancers using FDG PET-CT.

Methods: This retrospective study included 610 patients with various types of cancers. FDG PET-CT scans were used to measure FDG uptake in the liver, spleen, and bone marrow. Patients were grouped into hypoalbuminemia (< 3.5 g/dL) and normal albumin levels (≥ 3.5 g/dL). The study analyzed the correlation between serum albumin and SuVmax and SuVmean of the liver, spleen, and bone marrow.

Results: Patients with normal albumin levels exhibited significantly higher liver FDG uptake, with a mean Liver SuVmax of 3.73 ± 1.78 compared to 3.32 ± 0.75 in those with hypoalbuminemia ($p < 0.0001$). Similarly, Liver SuVmean was higher in the normal albumin group (2.17 ± 1.20) than in the hypoalbuminemia group (1.95 ± 0.48, $p = 0.0009$). No significant differences in FDG uptake were observed in the spleen and bone marrow between the two groups. The study found a weak positive correlation between albumin levels and liver FDG uptake, but no significant correlation with FDG uptake in the spleen and bone marrow.

Conclusion: Serum albumin levels are significantly associated with liver FDG uptake in patients with gastrointestinal cancers, suggesting that albumin may play a role in liver metabolism. However, albumin levels do not significantly impact FDG uptake in the spleen or bone marrow. These findings highlight the potential of albumin as a marker for liver metabolism in cancer patients but suggest that other factors influence the spleen and bone marrow.

Keywords: Albumin, FDG PET-CT, gastrointestinal cancers, liver metabolism, hypoalbuminemia

INTRODUCTION

Cancer continues to be a principal cause of morbidity and mortality globally, with patient outcomes being influenced by a multifactorial interplay of physiological and pathological variables. Among these variables, nutritional status, as assessed by biochemical markers such as serum albumin, has gained prominence as a critical factor in prognostication. Hypoalbuminemia, defined as a reduced concentration of serum albumin, is commonly observed in patients with malignancies and has been correlated with adverse clinical outcomes, including increased all-cause mortality (1-5).

Serum albumin is not merely a reflection of nutritional status in patients with cancer but also a marker of systemic inflammation and disease severity. Cancer patients frequently endure metabolic dysregulation, anorexia, and cachexia—conditions that impair protein synthesis and promote catabolic processes (3,4). Additionally, the systemic inflammatory response associated with malignancies can alter albumin metabolism, leading to decreased hepatic production and increased capillary permeability, which facilitates the extravasation of albumin into the interstitial space. Thus, hypoalbuminemia emerges not solely as a consequence of malnutrition but as a complex pathophysiological process intertwined with tumor biology and host response.

The integration of positron emission tomography/computed tomography (PET/CT) with 2-[18F]fluoro-

2-deoxy-D-glucose (FDG) leads a transformative advancement in clinical oncologic imaging (6). This approach provides a comprehensive acquisition of both glucose metabolism and anatomical imaging data, all within a single diagnostic session. FDG-PET/CT demonstrates its utility and versatility in enhancing patient care and management from initial staging to restaging, early treatment response assessment to metastatic disease evaluation, and even prognostication in intestinal cancer and diverse malignant tumors (6,7). Kitajima et al. claim that FDG-PET/CT results are excellent for evaluation of gastrointestinal cancers beyond local lymphadenopathy and metastatic disease, in their review (7).

The impact of serum albumin on liver, spleen and bone marrow FDG uptake in cancer patients is not clear. A previous study conducted by Otomi et al. revealed that FDG uptake in liver was lower in patients with malnutrition (8). In this regard, further studies are needed.

This study aims to investigate the albumin levels during the early stages of various types of cancers (gastric, pancreatic, lung, renal cell, etc.) and their impact on liver, spleen, and bone marrow FDG uptake.

METHODS

Study Design and Population

This retrospective cross-sectional study was conducted at Dicle University, School of Medicine, Department of Nuclear Medicine. The ethics approval was provided from the local clinical research ethics committee of Dicle University The Committee of Clinical Research (IRB no and date: 195/12.06.2024). This study was conducted according to the Declaration of Helsinki-Ethical principle for Human Researches. The data were obtained by investigating the hospital software system.

Case Selection and Exclusion

Case selection criteria encompassed patients referred to the nuclear medicine department for oncological evaluation, undergoing comprehensive whole-body PET-CT scans from January 1, 2021, to December 30, 2022. Inclusion criteria comprised individuals devoid of prior chemotherapy or radiotherapy, lacking surgical interventions, free from hematological malignancies, with laboratory analyses conducted within a week surrounding the PET/CT procedure. Patients undergoing PET-CT scans for restaging, treatment response assessment, or recurrence-metastasis investigation were excluded from the cohort. Furthermore, individuals presenting with hepatic or splenic metastases or primary tumors on PET-CT imaging were excluded. Additionally, patients with hematological malignancies or chronic inflammatory conditions like rheumatoid arthritis were not included in the study.

FDG PET-CT Scan

For FDG PET-CT imaging acquisition, patients were instructed to undergo a fast exceeding 6 hours, maintaining blood glucose levels below 140 mg/dL. Intravenous administration of FDG at a dosage of 0.1 mCi/kg was performed. Following injection, patients were confined to a specially lead-coated environment for 1 hour to facilitate tracer distribution. Subsequently, a total-body CT scan spanning from vertex to knees was conducted, succeeded by whole-body PET emission scanning. Imaging procedures were executed utilizing a Siemens Horizon PET/CT apparatus, model 2016, featuring 3D-TOF technology. The device boasted a 3 mm slice thickness, employing PET iterative and CT bp-LOR reconstruction methodologies for image generation. A low-dose CT device, utilized for anatomical delineation and attenuation correction, operated at 80 mA and 120 kV (Siemens Healthcare, GmbH, Henkestrasse 127, 91052 Erlangen, Germany). Evaluation of hepatic, splenic, and bone marrow metabolic activity was performed via SuVmax and SuVmean metrics extracted from FDG PET/CT scans.

Laboratory Assessment

Serum albumin and C-reactive protein (CRP) were noted. Those parameters were assessed for the potential association or correlation with SuVmax ve SuVmean of liver, spleen and bone marrow. Albumin <3.5 gr/dL was labeled as hypoalbuminemia.

STATISTICAL ANALYSIS

Data analysis was conducted using SPSS 15.0 for Windows statistical software. The distributions of continuous variables were assessed via the Kolmogorov-Smirnov test. Parametric variables were expressed as mean ± standard deviation and median (minimum and maximum), while categorical variables were presented as numbers and percentages. Correlation analysis, utilizing Pearson correlation coefficients, was employed to explore relationships between variables, evaluating the strength and direction of linear associations among continuous variables. Regression analysis was utilized to examine the influence of predictor variables (such as CRP, albumin, and ESR) on outcome variables (SuVmax and SuVmean of the liver, spleen, and bone marrow), encompassing both univariate and multivariate regression analyses. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the patients in this study was 58.7 ± 16.5 years. The gender distribution revealed that 55.3% of participants were male and 44.7% were female. A total of 610 cancer patients were assessed in this cohort, of which 24.43% had gastrointestinal cancers. Among the gastrointestinal cancers, pancreatic cancer was the most frequent, accounting for 29.53% of the cases

Table 1. The prevalence and features' of various types of cancers included in the study

Cancer Type	Age, years	Gender Male/female, n	Albumin, gr/dL	CRP, mg/dl
Gastrointestinal System Tumors				
Colon, n=39	60.28±13.47	22/17	3.52±0.81	2.3(0.09-127.17)
Rectum, n=23	52.22±13.77	10/13	3.81±0.59	5.39(0.08-47.76)
Stomach, n=26	61.23±11.85	13/13	3.26±0.97	1.21(0.04-137)
Pancreas, n=44	64.60±10.68	25/19	3.22±0.56	3.37(0.06-140.78)
Eosephagus, n=7	63.53±11.48	6/1	3.46±0.49	2.44(0.44-36.02)
Clatskin tumor, n=6	63.17±10.20	5/1	3.37±0.41	7.77(0.27-81.99)
GIST, n=4	59.00±15.85	3/1	3.69±0.28	0.49(0.13-3.54)
Extra-Gastrointestinal Tumors				
Lung, n=183	61.13±13.79	136/47	3.47±0.64	3.10(0.07-215.72)
Breast, n=67	51.66±13.22	1/66	4.16±0.41	0.43(0.04-61.97)
Mesothelioma, n=36	63.53±11.48	31/5	3.46±0.49	5.38(0.13-34.59)
Skin, squamous cell cancer, n=20	74.00±17.12	14/6	3.73±0.46	1.74(0.05-15.02)
Unknown Primary, n=147	60.77±17.10	74/73	3.37±0.67	2.60(0.02-245.23)
Nasophrayngeal, n=4	26.25±17.34	4/0	4.36±0.33	0.41(0.24-2.74)
Mediastinal mass, n=12	47.92±20.09	7/5	3.97±0.96	1.97(0.17-77.66)
Malign melanoma, n=7	59.00±25.89	4/3	3.74±0.57	0.35(0.08-3.01)
Laryngeal cancer, n=15	67.20±10.67	14/1	3.56±0.64	0.75(0.07-188.56)
Endometrium, over cancers, n=12	56.00±13.58	0/12	3.67±0.58	2.69(0.27-81.99)
Renal cell cancer, n=7	50.57±13.52	7/0	4.07±0.31	6.57(0.35-39.05)

(Table 1). The mean SuVmax and SuVmean values for FDG uptake in the liver, spleen, and bone marrow across different types of gastrointestinal cancers within this cohort are summarized in Table 2.

The Correlation Analysis (Albumin and SuVmax and SuVmean of Liver, Spleen and Bone Marrow)

The correlation coefficients for both Liver SuVmax (0.12) and SuVmean (0.11) with Albumin are relatively low, though they have statistically significant p-values (0.0112 and 0.0185, respectively) (Figure 1). This suggests a weak positive correlation between albumin levels and FDG uptake in the liver. Clinically, this might indicate that as albumin levels slightly increase, there is a modest increase in liver metabolic activity as measured by FDG uptake. However, the weak strength of this correlation implies that albumin is not a strong predictor of liver FDG uptake on its own and should be interpreted within the context of other clinical and metabolic factors.

The correlation between albumin and FDG uptake in the spleen (SuVmax= 0.05, SuVmean= 0.03) is very weak and not statistically significant (p-values of 0.3163 and 0.5312, respectively) (Figure 2). Clinically, this suggests that albumin levels do not have a meaningful impact on spleen FDG uptake. This lack of association might be expected, as spleen FDG uptake is often influenced by factors such as immune activation rather than albumin levels.

The correlations between albumin and bone marrow FDG uptake are negligible (SuVmax = 0.02, SuVmean = -0.05) and not statistically significant (p-values

Table 2. FDG Uptake in the Liver, Spleen, and Bone Marrow in different types of GIS cancers

Cancer Type	Liver, SuVmax and SuVmean	Spleen, SuVmax and SuVmean	Bone Marrow, SuVmax and SuVmean	SLR (Spleen-to-Liver Ratio)	BLR (Bone-to-Liver Ratio)
Colon, n=39	3.65±0.72 2.13±0.40	2.88±0.57 1.90±0.34	3.08±0.86 1.94±0.47	0.79±0.10 0.90±0.11	0.86±0.24 0.93±0.27
Rectum, n=23	3.55±0.77 1.96±0.46	2.80±0.57 1.77±0.36	3.20±0.88 2.00±0.53	0.79±0.09 0.91±0.13	0.92±0.29 1.05±0.32
Stomach, n=26	3.31±0.64 1.98±0.38	2.70±0.47 1.78±0.32	2.84±0.52 1.85±0.38	0.83±0.13 0.91±0.13	0.87±0.15 0.94±0.17
Pancreas, n=44	3.91±0.67 2.27±0.45	2.94±0.68 1.92±0.45	2.83±0.62 1.82±0.54	0.75±0.12 0.85±0.14	0.73±0.16 0.83±0.28
Eosephagus, n=7	3.55±0.63 2.11±0.34	3.20±0.71 1.95±0.47	3.11±0.69 1.85±0.48	0.90±0.14 0.92±0.14	0.87±0.28 0.87±0.14
Clatskin tumor, n=6	4.05±0.89 2.36±0.57	3.13±0.87 2.00±0.56	3.15±0.29 2.10±0.35	0.77±0.10 0.84±0.09	0.80±0.17 0.92±0.22
Gastrointestinal Stromal Tumor, n=4	3.57±0.60 2.22±0.55	3.55±1.31 2.12±075	3.17±1.45 2.00±0.86	0.97±0.23 0.94±0.17	0.86±0.28 0.88±0.23

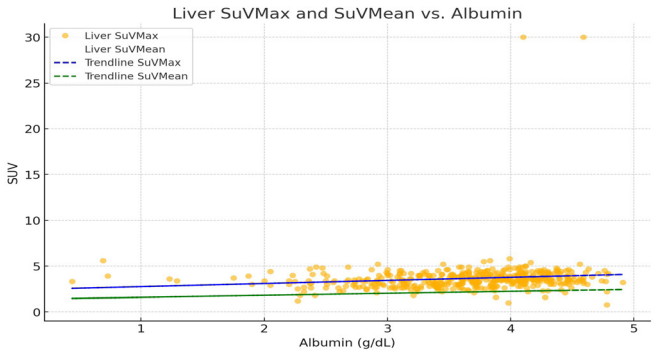

Figure 1. Scatter plot demonstrating the relationship between Albumin levels (g/dL) and FDG uptake in the liver, represented by SuVmax and SuVmean. The blue circles and green crosses depict individual data points for Liver SuVmax and SuVmean, respectively. Dashed lines indicate the trendlines for each parameter, illustrating a weak positive correlation between Albumin levels and FDG uptake in the liver.

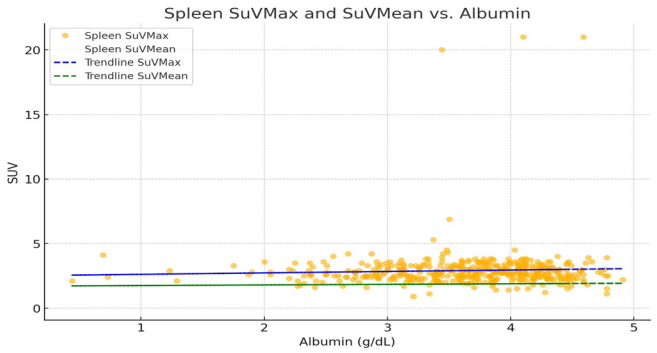

Figure 1. Scatter plot demonstrating the relationship between Albumin levels (g/dL) and FDG uptake in the spleen, represented by SuVmax and SuVmean. The blue circles and green crosses depict individual data points for Spleen SuVmax and SuVmean, respectively. Dashed lines indicate the trendlines for each parameter, illustrating the weak correlation between Albumin levels and FDG uptake in the spleen.

of 0.7294 and 0.2742, respectively) (**Figure 3**). This indicates no meaningful relationship between albumin levels and bone marrow metabolic activity. Clinically, bone marrow activity is more likely influenced by other factors such as hematopoietic activity, inflammation, or bone marrow pathology rather than by albumin levels.

Patients with normal albumin levels (≥3.5 g/dL) exhibited significantly higher liver FDG uptake, with a mean Liver SuVmax of 3.73 ± 1.78 compared to 3.32 ± 0.75 in those with hypoalbuminemia (p< 0.0001) (Table 3). Similarly, the Liver SuVmean was higher in the normal albumin group (2.17 ± 1.20) than in the hypoalbuminemia group (1.95 ± 0.48, p= 0.0009). However, there were no significant differences in spleen or bone marrow FDG uptake between the two groups. The Spleen SuVmax and SuVmean were similar in both groups (p= 0.8302 and p= 0.4283, respectively), as were the Bone Marrow SuVmax (p= 0.6784) and Bone Marrov SuVmean (p = 0.4420) (**Table 3**). These results suggest that albumin levels significantly impact liver metabolic activity but do not affect the spleen or bone marrow.

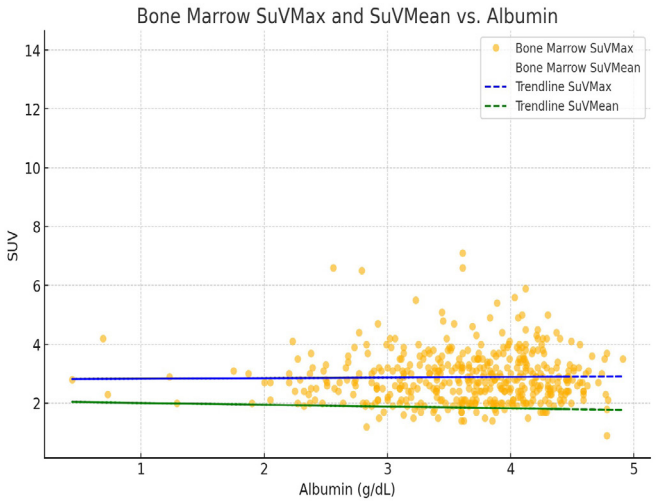

Figure 1. Scatter plot demonstrating the relationship between Albumin levels (g/dL) and FDG uptake in the bone marrow, represented by SuVmax and SuVmean. The blue circles and green crosses depict individual data points for Bone Marrow SuVmax and SuVmean, respectively. Dashed lines indicate the trendlines for each parameter, illustrating the lack of significant correlation between Albumin levels and FDG uptake in the bone marrow.

DISCUSSION

This study explored the relationship between serum albumin levels and FDG uptake in the liver, spleen, and bone marrow during the staging of gastrointestinal cancers using FDG PET-CT. The findings indicated a significant association between serum albumin levels and liver metabolic activity, with no significant impact on FDG uptake in the spleen or bone marrow. This highlights the potential of albumin as a marker for liver metabolism in cancer patients, emphasizing the importance of maintaining optimal nutritional and systemic conditions in this population.

Several studies have corroborated the findings regarding the influence of serum albumin on FDG uptake in gastrointestinal cancers. For instance, Song et al. examined the role of F-18 FDG PET/CT in predicting lymph node metastasis in gastric cancer and found that serum albumin levels, among other factors, were associated with FDG uptake in the liver, which further aligns with the current study's conclusion about

Table 3. Comparison of SUV parameters between hypoalbuminemia and normal albumin levels in the Liver, Spleen, and Bone Marrow in different types of GIS cancers

SUV Parameter	Hypoalbuminemia, n=89	Normal Albumin; n=60	p-value
Liver SuVmax	3.32 ± 0.75	3.73 ± 1.78	0.0000
Liver SuVmean	1.95 ± 0.48	2.17 ± 1.20	0.0009
Spleen SuVmax	2.86 ± 1.51	2.89 ± 1.30	0.8302
Spleen SuVmean	1.81 ± 0.43	1.86 ± 1.02	0.4283
Bone Marrow SuVmax	2.86 ± 0.87	2.89 ± 0.87	0.6784
Bone Marrov SuVmean	1.90 ± 1.10	1.83 ± 0.57	0.4420

albumin's role in liver metabolism. Elevated FDG uptake in the liver was often associated with better nutritional status, reflected by normal albumin levels (9).

Moreover, Lee et al. reported a clinical implication of FDG uptake in the bone marrow and liver on PET/CT in gastric cancer patients, noting a significant correlation between serum albumin levels and metabolic activity. This supports the idea that maintaining adequate albumin levels could play a role in optimizing liver function and potentially improving cancer outcomes (10).

On the contrary, some studies have not found a significant association between albumin and FDG uptake in organs like the spleen and bone marrow. Kim et al., in their study on diffuse splenic FDG uptake in rectal cancer patients, noted that albumin levels did not significantly correlate with FDG uptake in the spleen, suggesting that other factors such as immune regulation and systemic inflammation might play a more prominent role in influencing spleen metabolism (11). Additionally, Saito et al. examined FDG PET/CT imaging in gastrointestinal mantle cell lymphoma and observed no consistent pattern linking serum albumin with FDG uptake in the bone marrow, reinforcing the findings that albumin may not significantly impact the metabolic activity of bone marrow in these patients (12).

The collective evidence indicates that while serum albumin levels are associated with liver FDG uptake, they do not significantly affect FDG uptake in the spleen or bone marrow. The weak correlation observed in the current study, as well as in previous literature, suggests that liver metabolic activity is influenced by a complex interplay of factors, including but not limited to albumin levels. The differential impact on the spleen and bone marrow might be due to these organs' distinct physiological roles and regulatory mechanisms, such as cytokine activity and immune cell function, which are less dependent on albumin.

The findings demonstrate the potential of albumin as a marker for liver metabolism and the importance of maintaining adequate albumin levels in cancer patients. However, they also indicate that the metabolic activities in the spleen and bone marrow are regulated by other systemic and local factors. Future research should further explore these mechanisms and evaluate the prognostic implications of serum albumin in cancer metabolism and progression.

Limitations

The study has several limitations that should be acknowledged. First, its retrospective design inherently limits the ability to establish causality between albumin levels and FDG uptake in different organs. Retrospective studies are also prone to selection bias and confounding variables, which might have influenced the findings. Second, the sample size, although adequate for initial analysis, may not be sufficient to generalize the results to the broader population of patients with gastrointestinal cancers. The inclusion of various cancer types with potentially different metabolic behaviors further complicates the interpretation of albumin's impact across different organ systems.

Another limitation is the reliance on a single measurement of albumin and FDG uptake, which may not fully capture the dynamic changes in a patient's nutritional and metabolic status over time. Serum albumin levels can fluctuate due to various factors such as acute illness, inflammation, and therapeutic interventions, potentially confounding the results. Similarly, FDG uptake can be influenced by several factors including the tumor's metabolic activity, inflammatory response, and liver function, which were not controlled for in this study.

The study also did not account for other potential confounding factors that may influence FDG uptake, such as the presence of systemic inflammation, liver disease, or the use of medications that could alter metabolic activity. The absence of data on patient outcomes, such as survival rates, limits the ability to assess the prognostic significance of albumin in this context. Furthermore, the study's exclusion criteria, while necessary to reduce heterogeneity, may have resulted in the exclusion of patients with more advanced or complex disease, potentially biasing the findings toward a more favorable prognosis.

Lastly, the study did not explore the underlying mechanisms linking albumin to FDG uptake in the liver, spleen, and bone marrow. While the results suggest an association, they do not provide insight into the biological pathways involved. Future studies with a prospective design, larger sample sizes, and a more detailed examination of potential confounding variables are needed to validate these findings and elucidate the mechanisms by which albumin influences organ-specific metabolism in cancer patients.

CONCLUSION

This study demonstrates a significant association between serum albumin levels and FDG uptake in the liver during the staging of gastrointestinal cancers using FDG PET-CT. Patients with normal albumin levels showed higher liver FDG uptake, suggesting that albumin might play a role in modulating liver metabolic activity. In contrast, no significant association was found between serum albumin levels and FDG uptake in the spleen and bone marrow, indicating that these organs' metabolic activities are likely governed by different physiological and immunological factors.

DECLARATIONS

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Ethical Issues: This study was conducted in accordance with the Declaration of Helsinki and was approved by the local clinical research ethics committee of Dicle University (IRB no: 195 and date= 12.06.2024). Informed consent was obtained from all participants involved in this study. As this research involved a retrospective review of existing data, it posed minimal risk to participants, and no additional interventions were performed. There were no ethical issues encountered during the conduct of this study.

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AI: This study has benefited from the language revision and graphic processing provided by the latest Chat GPT-4.0; however, all final decisions have been made by the authors.

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Review

Targeted Treatment Strategies and Medication Management for Rheumatic Diseases During Pregnancy and Lactation: A Comprehensive Review

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Abstract

Pregnancy in women with immune-mediated rheumatic diseases poses significant challenges, including risks for both maternal and fetal adverse outcomes. This comprehensive review addresses the management of immune-mediated rheumatic diseases during pregnancy and lactation, focusing on medication strategies and treatment protocols to optimize pregnancy outcomes. The continuation or cessation of medications, including biologics and immunosuppressants, is a critical factor in managing disease activity while minimizing fetal risks. The review also explores the use of assisted reproductive technologies, fertility preservation methods for patients undergoing gonadotoxic treatments, and hormone replacement therapy. Additionally, the management of pregnancy in patients with conditions such as systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren's syndrome is discussed. Key recommendations from the American College of Rheumatology 2020 guidelines are provided, outlining best practices for medication use during pre-conception, pregnancy, and postpartum care. The review underscores the importance of individualized treatment plans and interdisciplinary collaboration to ensure favorable outcomes for both mother and child.

Keywords: Immune-mediated rheumatic diseases, pregnancy, preconception counseling, medication safety, autoimmune disorders in pregnancy

INTRODUCTION

Pregnancy in women with immune-mediated rheumatic diseases (IRD) can lead to serious maternal or fetal adverse outcomes (1). The prognosis of the disease is influenced by multiple factors, including the diagnosis, extent of disease activity and damage, treatments, and the presence of anti-Ro/SSA, anti-La/SSB, and antiphospholipid (aPL) antibodies (1-4). Although pregnancy may not exacerbate all inflammatory rheumatic diseases, it can aggravate some. Pre-pregnancy counseling is necessary to assess and reduce the risks of adverse pregnancy outcomes for each patient. Some medications need to be adjusted before, during, and/or after pregnancy. Postpartum disease flare-ups should be closely monitored (1-4).

Fertility rates in individuals with IRD are significantly lower than in the general population, largely influenced by both the underlying disease and the medications administered (5,6). Cyclophosphamide (CYC), in particular, is a leading agent associated with gonadal failure (7). For some patients, pregnancy may be contraindicated either due to active disease or the use of teratogenic medications, while for others, severe organ dysfunction with elevated maternal mortality risks may preclude pregnancy. In such cases, it is crucial to counsel patients on appropriate contraception methods, strategies to preserve gonadal function, and the potential use of assisted reproductive technologies.

Patients with IRD should conceive during periods of disease remission to reduce the risk of disease flare-ups during pregnancy, but the exact duration of this remission period remains a topic of debate (8). For patients with well-controlled disease, no extra-articular symptoms, and no organ dysfunction, three months of disease remission with stable pregnancy-safe medications is sufficient. However, in conditions such as systemic lupus erythematosus (SLE), the risk of disease flare-ups during pregnancy increases in patients who have had

active disease within the 4-6 months prior to conception, those who have active disease at the time of conception, and those who discontinue hydroxychloroquine (even if the disease is in remission) (9). The European League Against Rheumatism (EULAR) recommends a 6-12 month period of disease remission before pregnancy, depending on various maternal factors such as the degree of organ damage, if present (10).

A systematic review combined with a meta-analysis has shown that the disease activity of rheumatoid arthritis (RA) improves by 60% during pregnancy but worsens again by 50% postpartum (11). Psoriatic arthritis (PsA) data during pregnancy are relatively limited. However, available studies indicate that approximately one-third of cases remain stable throughout pregnancy, one-third experience disease exacerbation, and another one-third show improvement (12). The data on SpA is equally controversial, with very variable courses of disease (ranging from stable to exacerbated) reported during pregnancy. A recent study reported that spondyloarthritis (SpA) appears to be linked with an elevated risk of pregnancy complications, including preterm birth, delivering small for gestational age infants, preeclampsia, and an increased likelihood of caesarean section (13). During pregnancy, disease flare-ups may occur in about a quarter of SLE patients (9,14). In patients with antiphospholipid syndrome (APLS), the risk of thrombosis increases 2 to 10 times during pregnancy and the postpartum period (4,15). Women with Sjögren's syndrome are at a higher risk of experiencing complications during pregnancy. Research indicates a significant incidence of adverse fetal outcomes in these patients, including an increased risk of miscarriage, preterm birth, and neonatal complications such as congenital heart block due to the presence of maternal autoantibodies (16). In systemic sclerosis, the disease generally remains stable in most pregnancies (17). Women with pulmonary hypertension should avoid pregnancy on account of the high maternal mortality risk. The adverse pregnancy outcomes in various types of IRD are given in **Table 1.**

Anti-Ro (SS-A) and Anti-La (SS-B) autoantibodies cross the placental barrier through active transplacental transfer at the 16th week of pregnancy and reach to a maximum titer at 18-24 weeks of pregnancy (18). The interaction of these antibodies' Fc region with neonatal Fc receptors on syncytiotrophoblast cells can lead to a number of adverse effects for the fetus and newborn (19). Cardiac manifestations associated with autoimmune conditions may include congenital heart block (CHB), endocardial fibroelastosis, and dilated cardiomyopathy, which are referred to as neonatal lupus syndrome (20). In mothers who had AVB in previous pregnancies, this risk of recurrent CHB rises to around 17%. During vulnerable cardiac development stages (usually between week 16 and 24 of gestation) this may not just lead to myocarditis, cardiomyopathy and irreversible fibrotic remodeling of the AV node but can also lead to cutaneous signs of disease, hepatic damage and pancytopenias in the neonate. Since maternal anti-SSA/Ro and anti-La (SS-B) antibodies are cleared from the infant's circulation, most of these symptoms resolve within the first 6-9 months of life (18-20).

Persistent positivity for aPL antibodies, such as B2-glycoprotein, anticardiolipin, and lupus anticoagulant, can lead to specific adverse pregnancy outcomes (21,22). These include one or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation, preterm birth before 34 weeks due to eclampsia, preeclampsia, or placental insufficiency, and three or more consecutive spontaneous pregnancy losses before 10 weeks of gestation, unexplained by chromosomal abnormalities, maternal anatomical or hormonal factors. Maternal thrombosis, which characterizes antiphospholipid syndrome, may also develop. Among these, lupus anticoagulant is the strongest antibody linked to adverse pregnancy outcomes. The concurrent presence of all three antibodies during pregnancy constitutes the highest risk (4,15,21,22).

The presence of organ dysfunction as a complication of inflammatory rheumatic diseases (IRD) significantly increases the likelihood of maternal and fetal morbidity and mortality, and therefore, it should be discussed during pregnancy planning. If a patient has active disease and organ dysfunction, conception should be postponed until disease remission and the improvement

Table 1. Adverse pregnancy outcomes in various types of IRD

Disease	Adverse Pregnancy Outcomes	Risk Factors
Rheumatoid Arthritis	Pregnancy-related hypertension, intrauterine growth restriction, preterm birth, small-for-gestational-age infants, low birth weight	Active disease during conception and pregnancy
Axial Spondyloarthritis	Increased risk of preterm birth, small-for-gestational-age infants, emergency or elective cesarean section	Active disease during conception and pregnancy
Systemic Lupus Erythematosus, Sjögren Syndrome , Antiphospholipid Syndrome	Pregnancy loss, pregnancy-related hypertension, intrauterine growth restriction, preterm birth, small-for-gestational-age infants, low birth weight, cesarean section, congenital heart block, neonatal lupus	Active disease, hypertension, lupus nephritis, antiphospholipid antibodies (triple positivity for anticardiolipin, B2-glycoprotein I, lupus anticoagulant), anti-SSA/Ro, anti-SSB/La antibodies
Scleroderma	Increased risk of preterm birth, intrauterine growth restriction	Presence of rapidly progressive diffuse disease

or normalization of organ function are achieved. For instance, the presence of active lupus nephritis at the time of conception is a strong indicator of adverse maternal and fetal outcomes (23). However, the risks associated with kidney disease are not exclusive to patients with rheumatic diseases. Prospective studies involving women with chronic kidney disease (CKD) from various etiologies have shown an increased risk of preeclampsia, preterm birth, small-for-gestational-age infants, and higher neonatal and perinatal risks (24). Additionally, women with advanced CKD (stages 4-5) prior to pregnancy are at risk of accelerated renal function decline, which may progress to end-stage renal disease and necessitate kidney replacement therapy during pregnancy or in the postpartum period (24,25).

Other relative contraindications for pregnancies associated with IRD that necessitate multidisciplinary consultation and management include pulmonary hypertension unresponsive to treatment, severe interstitial lung disease, advanced heart failure, and a history of severe gestational hypertensive disorders. For these reasons, IRD patients require careful monitoring by a multidisciplinary team regarding contraception, pregnancy, and breastfeeding (including medications), assisted reproductive technologies (ART), fertility preservation, and hormone replacement therapy (HRT). To address this need, the American College of Rheumatology (ACR) published the latest guidelines in 2020 on the management of reproductive health in patients with rheumatic and musculoskeletal diseases (10). A summary of this guideline is provided below.

ACR 2020 RECOMMENDATIONS (10)

Contraception

For women with IRD (immune-mediated rheumatic diseases) should prioritize highly effective methods like IUDs or subdermal progestin implants. Emergency contraception, such as levonorgestrel, is recommended for all patients, including those with SLE or positive aPL antibodies, due to the lower risk compared to unplanned pregnancy (10).

For SLE patients with stable or low disease activity and negative aPL antibodies, IUDs and progestin implants are preferred, while estrogen-containing methods should be avoided due to thrombosis risk. In SLE patients with moderate or severe disease or nephritis, progestin-only or IUD contraceptives are advised, avoiding estrogen-containing methods.

Women with positive aPL antibodies should avoid combined estrogen-progestin contraceptives due to the increased thromboembolism risk, favoring IUDs or progestin-only options. Long-term use of depot medroxyprogesterone acetate (DMPA) is discouraged for women at risk of osteoporosis. For those on mycophenolate mofetil/mycophenolic acid (MMF), IUDs or combined contraceptive methods are recommended to counter the potential reduced efficacy of oral contraceptives (10).

Assisted Reproductive Technology (ART)

Assisted reproductive technology (ART) is strongly recommended for women with IRD who have stable or remission disease, are aPL antibody-negative, and are on pregnancy-compatible medications (10,26,27). However, for patients with moderate to severe disease activity, postponing ART is recommended due to the increased pregnancy risks associated with active IRD. A 6-month period of stable, inactive, or low-level disease is advised for pregnancy planning, though individual factors may vary.

In SLE patients, there is concern that ovarian stimulation might exacerbate active disease, but increasing prednisone during ART procedures is generally not recommended. Instead, treatment should be based on disease monitoring.

For subfertile patients with stable disease, asymptomatic aPL antibodies, obstetric APS, or treated thrombotic APS, ART with anticoagulation is conditionally recommended:

- For asymptomatic aPL antibody-positive patients, prophylactic anticoagulation with heparin or LMWH is recommended during ART.
- For women with obstetric APS, prophylactic anticoagulation is recommended, and for those with thrombotic APS, therapeutic anticoagulation is advised during ART.

Embryo and Oocyte Cryopreservation

For patients with stable conditions undergoing ovarian stimulation for oocyte or embryo cryopreservation, continuing necessary immunosuppressive or biological therapies is strongly recommended, except for CYC, which affects maturing follicles.

Fertility Preservation in Women with IRD Treated with CYC

In premenopausal women receiving monthly intravenous CYC, co-therapy with gonadotropin-releasing hormone agonists is conditionally recommended to prevent primary ovarian failure.

Fertility Preservation in Men with IRD Treated with CYC

Testosterone co-therapy is conditionally not recommended for men on CYC as it has been ineffective in preserving fertility during chemotherapy. Sperm cryopreservation before treatment is strongly recommended for men undergoing CYC therapy who wish to preserve fertility.

Hormone Replacement Therapy (HRT)

- For women with SLE who are aPL-negative and have

severe vasomotor symptoms, HRT is conditionally recommended if there are no contraindications.
•In asymptomatic women with aPL, HRT is conditionally not recommended.
•HRT is strongly discouraged for women with obstetric and/or thrombotic APS.
•In APS patients on anticoagulation or those previously aPL-positive but now negative, HRT is conditionally not recommended. However, for women with a history of aPL positivity but no clinical APS history, HRT may be conditionally considered. If the goal of ovarian stimulation is to induce oocyte development for oocyte or embryo cryopreservation, it is strongly recommended to continue necessary immunosuppressive and/or biological therapies in patients with stable conditions, with the exception of CYC, which directly affects maturing follicles.

Pre-Pregnancy Counseling and Medication Adjustments

Women with IRD who are planning a pregnancy should receive counseling on how to improve maternal and fetal outcomes, as supported by numerous studies. These women should be followed closely by specialists in obstetrics-gynecology, maternal-fetal medicine, and neonatology as needed.

For women on medications incompatible with pregnancy, transitioning to pregnancy-safe drugs is recommended, allowing enough time to evaluate the effectiveness and tolerability of the new medication. Pregnant women with active IRD requiring treatment should use pregnancy-compatible steroid-sparing agents, as both active disease and prolonged high-dose glucocorticoids pose risks to the mother and fetus.

For women with SLE or related conditions (e.g., Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis), testing for anti-Ro/SSA and anti-La/SSB antibodies before pregnancy or early in pregnancy is recommended. Repeating these tests during pregnancy is not advised due to the stability of antibody titers.

Patients with Scleroderma Renal Crisis (SRC)

In cases of active SRC during pregnancy, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are strongly recommended, as the risk of untreated SRC outweighs the risks associated with these medications during pregnancy (28,29).

Patients with SLE

Women with SLE planning to become pregnant, or who are already pregnant, should be tested for lupus anticoagulant (LA), anticardiolipin (aCL), and anti-B2 glycoprotein I antibodies before or early in pregnancy, without repeating the tests during pregnancy. Hydroxychloroquine (HCQ) should be taken during pregnancy by all women with SLE, if possible (30). If already on HCQ, continuation is strongly recommended, and if not, starting HCQ is conditionally advised, barring contraindications. Additionally, starting low-dose aspirin (81 or 100 mg daily) from the first trimester is conditionally recommended (10). As active disease impacts maternal and pregnancy outcomes, monitoring SLE disease activity every three months through clinical history, physical exams, and lab tests is strongly recommended for good practice.

Patients with Positive Antiphospholipid Antibodies (aPL)

For pregnant women who are aPL antibodies-positive but do not meet the criteria for obstetric or thrombotic APS, prophylactic aspirin (81 or 100 mg per day) is recommended during pregnancy to prevent preeclampsia (10). For patients with obstetric APS, a combination of low-dose aspirin and prophylactic-dose heparin (typically low molecular weight heparin, LMWH) is strongly recommended. Additionally, for women with obstetric APS, prophylactic anticoagulation for 6-12 weeks postpartum is also advised. For pregnant women with thrombotic APS, treatment with low-dose aspirin and therapeutic-dose heparin (usually LMWH) during pregnancy and the postpartum period is strongly recommended (10,31). However, for aPL-positive patients who do not meet the criteria for obstetric APS, combining prophylactic-dose heparin with low-dose aspirin is not recommended. In cases of pregnancy loss despite standard treatment with low-dose aspirin and prophylactic heparin or LMWH, the use of intravenous immunoglobulin (IVIG) or increased doses of LMWH is conditionally not recommended due to lack of significant benefit. The addition of prednisone to prophylactic-dose heparin or LMWH and low-dose aspirin is strongly not recommended, as no controlled studies demonstrate its benefit. For patients with primary APS, adding HCQ to prophylactic-dose heparin or LMWH and low-dose aspirin is conditionally recommended. In pregnant women who are aPL-positive but do not meet APS criteria and have no other medical indication (e.g., SLE), prophylactic HCQ is conditionally not recommended (10).

Anti-Ro/SSA and/or Anti-La/SSB Antibodies During Pregnancy

For pregnant women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies but have no history of a baby with CHB or neonatal lupus erythematosus (NLE), serial fetal echocardiography starting between 16 and 18 weeks is recommended, with less frequent intervals (though the specific interval is not determined) (10). For women with a previous baby with CHB or other forms of NLE, weekly fetal echocardiography from 16-18 weeks until 26 weeks is conditionally recommended. HCQ is conditionally recommended for all pregnant women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies. For those with first or second-

degree fetal heart block detected on echocardiography, treatment with oral dexamethasone (4 mg per day) is recommended. However, if CHB (without other heart inflammation) is present, the use of dexamethasone is conditionally not recommended.

MEDICATION USE

Before conception, CYC and thalidomide are not recommended for men. CYC can impair spermatogenesis or be mutagenic, and should be discontinued at least three months before conception (10,32). Thalidomide, a potent teratogen detectable in seminal fluid, should be discontinued at least one month prior to conception. For men with IRD planning fatherhood, the continuation of hydroxychloroquine (HCQ), azathioprine, 6-mercaptopurine, colchicine, and tumor necrosis factor inhibitors is strongly recommended. Continuation of methotrexate (MTX), mycophenolate mofetil (MMF), leflunomide, sulfasalazine, calcineurin inhibitors, and NSAIDs is conditionally recommended, despite MTX labels suggesting discontinuation due to lack of evidence of mutagenesis or teratogenicity. Sulfasalazine may affect sperm quality, but is not linked to teratogenicity, so its continuation is conditionally recommended. If conception is delayed, semen analysis is advised. Limited evidence supports the conditional continuation of anakinra and rituximab (Table 2).

It is recommended to discuss medication use with patients before conception, especially for those starting treatments that affect gonadal function, such as CYC. Teratogenic drugs like MTX, MMF, CYC, and thalidomide should be discontinued at least three months before conception. For women on leflunomide, a cholestyramine washout is recommended before conception or upon pregnancy confirmation if serum metabolites are present. If serum metabolites are undetectable, the risk of pregnancy loss or birth defects does not increase. For life-threatening conditions in the second or third trimester, CYC may be conditionally recommended (10).

After stopping teratogenic drugs, a period of observation is advised to ensure disease stability after transitioning to pregnancy-compatible medications or going drug-free. If a woman is accidentally exposed to teratogenic drugs, referral to a maternal-fetal medicine specialist or genetic counselor is strongly recommended (10) (Table 3).

Medications such as HCQ, azathioprine/6-mercaptopurine, colchicine, and sulfasalazine are safe during pregnancy and should be continued. Calcineurin inhibitors (tacrolimus and cyclosporine) and NSAIDs are conditionally recommended for pregnancy use, but NSAID discontinuation before conception is advised if fertility issues arise, as NSAID-induced unruptured follicle syndrome may cause subfertility. NSAIDs should be avoided in the third trimester to prevent premature closure of the ductus arteriosus, and non-selective NSAIDs are preferred over COX-2 inhibitors in early pregnancy (10,33).

Low-dose glucocorticoid therapy (≤10 mg prednisone per day) is recommended during pregnancy if clinically necessary. If a higher dose is required, adding a steroid-sparing agent is advised to keep glucocorticoid doses below 20 mg per day. Stress-dose glucocorticoids are not routinely recommended for vaginal deliveries, but they may be conditionally recommended for cesarean deliveries.

Tumor Necrosis Factor Inhibitors (TNFi) During Pregnancy

The continuation of tumor necrosis factor inhibitor (TNFi) therapy with infliximab, etanercept, adalimumab, or golimumab before and during pregnancy is conditionally recommended (10). Certolizumab, which lacks an Fc chain and has minimal placental transfer, is strongly recommended to continue before and during pregnancy.

Table 2. Medication safety during pregnancy and lactation in IRD patients

Medication	Safety Category	Recommendation
Hydroxychloroquine (HCQ)	Safe	Strongly recommended throughout pregnancy
Azathioprine/6-Mercaptopurine	Safe	Strongly recommended throughout pregnancy
Colchicine	Safe	Strongly recommended throughout pregnancy
Sulfasalazine	Safe	Strongly recommended throughout pregnancy
Tumor Necrosis Factor Inhibitors (Infliximab, Adalimumab, Etanercept)	Safe	Conditionally recommended before and during pregnancy; discontinue in 3rd trimester if disease is well-controlled
Certolizumab	Safe	Strongly recommended throughout pregnancy due to minimal placental transfer
Calcineurin Inhibitors (Tacrolimus, Cyclosporine)	Safe	Conditionally recommended during pregnancy
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Conditional	Discontinue before conception if subfertility; not recommended in 3rd trimester due to risk of ductus arteriosus closure
Methotrexate (MTX)	Unsafe	Strongly recommended to discontinue 3 months before conception
Mycophenolate Mofetil (MMF)	Unsafe	Strongly recommended to discontinue 3 months before conception
Cyclophosphamide (CYC)	Unsafe	Strongly recommended to discontinue 3 months before conception; can be used in life-threatening conditions during 2nd/3rd trimester
Thalidomide	Unsafe	Strongly recommended to discontinue 1 month before conception

Table 3. Preconceptional counseling for IRD patients

Counseling Aspect	Recommendation
Medication Review	Evaluate current medications and discontinue teratogenic drugs (e.g., MTX, MMF, CYC, Thalidomide) at least 3 months before conception.
Disease Activity	Ensure disease is in remission for at least 6-12 months before attempting pregnancy.
Fertility Preservation	Discuss fertility preservation options for patients undergoing gonadotoxic therapies (e.g., CYC).
Contraception	Recommend effective contraceptive methods (e.g., IUDs, progestin implants) for women who are not planning pregnancy.
Assisted Reproductive Technologies (ART)	For women with stable IRD and on pregnancy-compatible medications, ART is an option. Delay ART in cases of moderate to severe disease activity.
Hydroxychloroquine (HCQ)	Strongly recommended for women with SLE or related conditions to maintain disease control during pregnancy.
Risk of Flares	Counsel on the increased risk of disease flare-ups postpartum and ensure a management plan is in place.
Thromboembolism Risk	For women with positive aPL antibodies or APS, consider prophylactic anticoagulation therapy during pregnancy.
Monitoring	Recommend regular monitoring of disease activity and organ function throughout pregnancy.
Genetic Counseling	For women at risk of congenital heart block or neonatal lupus (anti-Ro/SSA, anti-La/SSB positive), consider genetic counseling and serial fetal echocardiography.

The placental transfer and fetal exposure of most biological therapies depend on the stage of pregnancy. Most IRD biological therapies, containing an Fc IgG1 structure, do not significantly pass into fetal circulation until the second trimester. In the third trimester, TNF inhibitors with the IgG1 Fc structure (infliximab, etanercept, adalimumab, and golimumab) show significant placental transfer, leading to substantial drug levels in the newborn. Although limited evidence indicates no adverse effects from these TNF inhibitors, particularly during the first trimester, the 'Voting Panel' concluded that if the disease is well-controlled, TNF inhibitors can be discontinued in the third trimester. However, if the disease remains active, TNF inhibitors may be continued through delivery, though newborns will likely have significant serum drug levels for some time after birth.

Other Biologics

There is limited data on the compatibility of non-TNF biologics with pregnancy. Since most of these agents likely do not cross the placenta until the second trimester, the panel conditionally recommends that IgG-based non-TNF biologics can be considered compatible during the periconception period but should be discontinued as soon as pregnancy is confirmed (with the first positive pregnancy test). For women attempting to conceive, the continuation of therapies such as anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab is conditionally recommended (34). However, these therapies should be discontinued once pregnancy is confirmed. If disease control cannot be maintained with medications compatible with pregnancy, it is important for the physician and patient to discuss the risks of uncontrolled disease during pregnancy compared to the potential risks posed by continuing these medications.

Rituximab

For women trying to conceive, the continuation of rituximab is conditionally recommended, especially in cases where there is life- or organ-threatening disease activity, and it may also be continued during pregnancy. However, the use of this medication during the second half of pregnancy increases the risk of the neonate being born with reduced B cell levels at birth (34).

Small Molecule Agents

As there is no current evidence regarding the use or safety of newer small-molecule agents such as tofacitinib, baricitinib, and apremilast during pregnancy, the 'Voting Panel' chose not to make specific recommendations about these drugs. However, it is likely that small molecules can cross the placenta.

Targeted Treatment Strategy for IRD During Pregnancy (10)

SLE or other autoimmune diseases:

- •Baseline treatment: Low-dose aspirin, hydroxychloroquine, vitamin D ± low-dose glucocorticoids.
- •Modifications for moderate disease flare-ups: Azathioprine ± cyclosporine, ± tacrolimus, ± moderate-dose glucocorticoids.
- •Modifications for severe disease flare-ups: High-dose glucocorticoids, ± cyclophosphamide, ± plasmapheresis, ± IVIG.

RA or other inflammatory arthritis:

- •Baseline treatment: Hydroxychloroquine, ± sulfasalazine, ± TNF inhibitor, vitamin D.
- •Modifications for moderate disease flare-ups: Low-dose glucocorticoids, ± other biologic DMARDs.
- •Modifications for severe disease flare-ups: High-dose glucocorticoids, ± cyclosporine, ± tacrolimus.

APS:

- •Baseline treatment: Low-dose aspirin, LMWH, vitamin D.
- •Recurrent obstetric APS: Hydroxychloroquine.
- •Recurrent thrombosis or catastrophic APS: Rituximab, ± IVIG, ± plasmapheresis (Note: Recommendations from a 2019 review, differing from ACR-2020 guidelines).

Medication Use Recommendations for Men with IRD Planning to Have Children

•Strongly recommended to continue: Azathioprine/6-mercaptopurine, colchicine, hydroxychloroquine, all TNF inhibitors.
•Conditionally recommended to continue: Anakinra, COX-2 inhibitors, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil, mycophenolic acid, NSAIDs, rituximab, sulfasalazine (if conception does not occur, perform semen analysis), tacrolimus.
•Strongly not recommended to continue: Cyclophosphamide (should be discontinued 12 weeks before conception).
•Conditionally not recommended to continue: Thalidomide (should be discontinued 4 weeks before conception).
•No recommendation due to limited data: Abatacept, apremilast, baricitinib, belimumab, secukinumab, tocilizumab, tofacitinib, ustekinumab.

Maternal Medication Use Overview of medication use before and during pregnancy and lactation

•If planning pregnancy: Discuss medication use, including CYC (best clinical practice: BCP).
•If pregnant and exposed to teratogenic drugs: Immediately discontinue drugs and seek counseling (BCP).
•If experiencing difficulty conceiving, discontinue NSAIDs (conditional recommendation). Avoid NSAIDs in the third trimester (strong recommendation).
•Prefer NSAIDs over COX-2 inhibitors (conditional recommendation).
•Discontinue MTX, MMF, thalidomide, and CYC before conception (strong recommendation).
•Use CYC only in the second and third trimesters in life-threatening diseases (conditional).
•Discontinue leflunomide 24 months before conception or check serum metabolite levels and treat with cholestyramine washout (strong recommendation).
•Continue HCQ, sulfasalazine, AZA, colchicine (strong recommendation). Continue cyclosporine and tacrolimus (conditional). Continue certolizumab (strong recommendation).
•Continue infliximab, etanercept, adalimumab, golimumab (conditional recommendation).
•Discontinue rituximab, belimumab, anakinra, abatacept, tocilizumab, secukinumab, ustekinumab when pregnancy is confirmed (conditional recommendation).
•Use rituximab during pregnancy in cases of organ or life-threatening disease (conditional recommendation).
•No recommendations for tofacitinib, baricitinib, apremilast due to lack of data. Continue regular low-dose prednisone (conditional recommendation).
•Reduce high-dose prednisone by adding pregnancy-compatible medications if necessary (strong recommendation).
•Stress-dose steroids at delivery: not recommended for vaginal delivery, conditionally recommended for cesarean (conditional).
•Encourage breastfeeding and maintain disease control with compatible medications if possible (BCP).

Medications Compatible with Breastfeeding

•Strong recommendation: HCQ, infliximab, etanercept, adalimumab, golimumab, certolizumab, rituximab.
•Conditional recommendation: NSAIDs, sulfasalazine, colchicine, AZA, cyclosporine, tacrolimus, anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab.
•Strong recommendation: Prednisone or non-fluorinated steroid equivalent <20 mg daily. For daily doses ≥20 mg, discard breast milk collected within 4 hours of taking the medication.
•Strongly not recommended: Leflunomide, MMF, CYC, thalidomide.
•Conditionally not recommended: MTX.

Recommended TNF Inhibitor Discontinuation Timing During Pregnancy

•Infliximab: 16-20 weeks.
•Etanercept: 24-32 weeks.
•Adalimumab: 20-24 weeks.
•Certolizumab: Safe throughout pregnancy.
•Golimumab: Limited information; likely safe in the first trimester.

Limitations of the Review

The review relies heavily on existing literature, which may be subject to publication bias or varying quality of evidence. Data on some rheumatic diseases during pregnancy and lactation, such as PsA and SpA, is limited, reducing the ability to generalize findings across all types of inflammatory rheumatic diseases. Some recommendations for medication management during pregnancy are based on limited evidence or expert opinion, especially regarding newer biologics and small-molecule agents. The review did not include direct patient data or clinical trials, making it more reliant on theoretical conclusions and previous studies.There may be regional differences in the availability of medications and clinical guidelines that were not fully addressed in the review.

Strengths of the Review

The review provides a comprehensive overview of medication safety and treatment strategies during pregnancy and lactation for women with inflammatory rheumatic diseases, summarizing key guidelines and recommendations. It covers a wide range of immune-mediated rheumatic conditions, including SLE, rheumatoid arthritis, antiphospholipid syndrome, and Sjögren's syndrome. The inclusion of detailed

recommendations from the American College of Rheumatology (ACR) 2020 guidelines provides a valuable resource for clinicians in managing pregnant and lactating patients with rheumatic diseases. The review emphasizes the importance of individualized treatment plans and interdisciplinary collaboration to optimize outcomes for both mother and child. It highlights both the need for pre-conception counseling and the management of disease flares during pregnancy, providing practical insights into clinical care.

CONCLUSION

This comprehensive review underscores the complexity of managing inflammatory rheumatic diseases during pregnancy and lactation, emphasizing the need for individualized treatment strategies. Key takeaways include the critical importance of pre-conception counseling and the management of disease activity to optimize both maternal and fetal outcomes. Women with well-controlled disease prior to conception generally experience better pregnancy outcomes, while active disease increases the risk of complications such as preterm birth, intrauterine growth restriction, and maternal mortality.

The safety of medications during pregnancy and lactation is a focal point, with clear guidelines favoring certain immunosuppressants, biologics, and anti-inflammatory agents over others. Drugs such as hydroxychloroquine, azathioprine, and certolizumab are recommended during pregnancy due to their favorable safety profiles, while medications like methotrexate and mycophenolate mofetil should be discontinued well before conception due to their teratogenic risks.

The review also highlights the importance of interdisciplinary collaboration, involving rheumatologists, obstetricians, and maternal-fetal medicine specialists, to ensure that both disease control and pregnancy management are aligned. Continuous monitoring during pregnancy and postpartum, coupled with personalized medication adjustments, is essential to mitigate the risks of disease flare-ups and adverse pregnancy outcomes.

DECLARATIONS

Ethics: In this review, the authors declare that there are no ethical concerns or conflicts of interest. All authors have contributed to the review in accordance with ethical standards, and no part of the study has involved any activities that could raise ethical issues. Additionally, the authors confirm that there are no financial or personal relationships that could be perceived as a conflict of interest in the preparation or publication of this review. All decisions and interpretations have been made independently, with no influence from any external funding sources, institutions, or commercial entities.

AI: This review used the language revision and structural improvement processes provided by the latest Chat GPT-4.0; however, all final decisions have been made by the authors.

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Letter to Editor

17q12 Deletion Syndrome with Convulsions and Family History of Increased Intracranial Pressure Syndrome

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To The Editor

We present a case of a 5.5-year-old boy diagnosed with 17q12 deletion syndrome, a rare genetic disorder that manifests in a variety of clinical symptoms, including neurological and renal abnormalities (1). We aim to underscore the importance of recognizing early clinical signs and implementing appropriate genetic testing and management.

The child experienced his first convulsion at 8 months, followed by additional seizures at 11 and 14 months, leading to the initiation of levetiracetam at a dosage of 10 mg/kg 2x1 daily (currently on 25 mg/kg 2x1). Despite these early seizures, his developmental milestones have been normal, and no developmental delay has been observed. At the age of 4, bilateral renal cysts were detected through routine imaging, a hallmark feature of 17q12 deletion syndrome due to the involvement of the HNF1B gene.

The clinical course includes an abnormal EEG conducted 1.5 years ago, revealing patterns suggestive of underlying neurological issues. This, coupled with the patient's history of seizures, prompted further investigations. Ultimately, the 17q12 deletion was confirmed through genetic testing, via chromosomal microarray analysis.

It was noted that the mother has been on acetazolamide therapy since the age of 18 due to 17q12 deletion syndrome with convulsions and family history of increased intracranial pressure syndrome syndrome and has intermittently received treatment for migraines associated with severe headaches. The parents and siblings were also evaluated through genetic testing, given the possibility of autosomal dominant inheritance, to identify asymptomatic carriers or those at risk for complications (test results are awaiting).

Key Clinical Features of This Case:

•Seizures: The child had three seizure episodes by the age of 14 months. Despite these, there have been no recurrent seizures since initiating levetiracetam levetiracetam.

•Abnormal EEG: The detection of an abnormal EEG pattern led to the decision to pursue genetic testing, which confirmed the presence of the 17q12 deletion.

•Renal Cysts: Bilateral renal cysts were discovered at age 4, consistent with the deletion's impact on the HNF1B gene, known for its role in renal development and function.

•No Developmental Delay: Despite the genetic diagnosis and seizure history, the child exhibits no signs of developmental delay, which is notable given the syndrome's variability in neurodevelopmental impact.

•Extrarenal monitoring: The patient is being closely monitored for possible future extrarenal manifestations, such as endocrine disorders like diabetes, that are associated with this genetic syndrome.

Management:

1.Neurological Care: The patient remains on Keppra to prevent seizure recurrence, and regular neurological assessments are advised to monitor for any changes in cognitive or motor function.

2.Renal Monitoring: The child is undergoing biannual renal evaluations, including ultrasound and serum creatinine tests, to track cyst progression. If the cysts significantly enlarge or impair renal function, future interventions like cyst drainage or nephrectomy may be considered.

3.Genetic Counseling: The family was informed about inheritance patterns and the potential for the condition to be passed on. Prenatal and preimplantation genetic testing options were discussed, and the family was offered psychological support for coping with the long-term implications

of the diagnosis.

This case demonstrates the importance of early recognition of the diverse manifestations of 17q12 deletion syndrome. Although the child has no developmental delays, his history of seizures, abnormal EEG findings, and renal cysts reflect the syndrome's broad clinical spectrum. Early diagnosis through genetic testing allows for timely interventions, particularly in managing seizure activity and monitoring renal health.

17q12 deletion syndrome is a chromosomal disorder resulting from the deletion of a segment on the long arm (q12) of chromosome 17. This deletion leads to a diverse spectrum of clinical manifestations that can vary significantly, even among affected individuals within the same family. A hallmark feature of this syndrome is the involvement of the renal and urinary systems, ranging from severe congenital malformations that can result in renal failure in utero, to milder or asymptomatic presentations. Renal cysts are particularly prevalent in affected individuals. The syndrome is also associated with the development of maturity-onset diabetes of the young type 5 (MODY5), which typically arises before the age of 25 and is attributed to pancreatic dysfunction. The combination of renal cysts and MODY5 is referred to as renal cysts and diabetes (RCAD) syndrome. Approximately 50% of individuals with 17q12 deletion syndrome exhibit developmental delays, particularly in speech and language, intellectual disabilities, or psychiatric conditions such as autism spectrum disorder, schizophrenia, anxiety, and bipolar disorder. Less commonly, abnormalities in other organ systems, including the eyes, liver, brain, and genitalia, are observed. In females, this may present as Mayer-Rokitansky-Küster-Hauser syndrome, characterized by underdevelopment or absence of the uterus and vagina. Additionally, subtle craniofacial dysmorphisms are sometimes noted. The phenotypic expression of 17q12 deletion syndrome is highly variable, underscoring the complexity of its clinical presentation (3).

We hope that this case adds to the growing body of literature on 17q12 deletion syndrome and encourages clinicians to consider genetic testing in cases of unexplained neurological and renal abnormalities in children.

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DECLARATIONS

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