INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 13; Issue 3; March 2024; Page No.2895-2900
DOI: http://dx.doi.org/10.24327/ijcar.2024.2900.1631

Research Article

ROLE OF SERUM IGG AS A PROGNOSTIC MARKER IN CHRONIC LIVER DISEASE IN A TERTIARY CARE CENTRE

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A R T I C L E I N F O

Article History:
Received 10th February, 2023
Received in revised form 28th February, 2024
Accepted 16th March, 2024
Published online 28th March, 2024

Key words:

Cirrhosis, Serum IgG, Hypergammaglobulinemia, MELD, Portal hypertension

A B S T R A C T

Decompensated liver cirrhosis induces functional immunosuppression, characterized by an increased susceptibility to infections and a failure to mount protective immune responses to prophylactic vaccinations. The role of Serum IgG levels, a cost-effective and readily available test, in predicting outcomes in cirrhosis and assessing humoral immune capacity, has been inadequately studied, with limited research available on this aspect. 100 consecutive cirrhotic patients admitted to our hospital between April 2022 to December 2023, encompassing compensated, decompensated cirrhosis and acute-on-chronic liver disease cases were included in the study.. Serum IgG levels were measured and patients were prospectively followed for 12 months, and the correlation between serum IgG levels and prognostic outcomes was assessed.Statistical analysis was conducted using SPSS version 20. Mean serum IgG was 1.26-fold higher than normal but did not correlate with the severity of liver disease according to MELD/CHILD score. Hypergammaglobulinemia was present in 36.58% of decompensated cirrhosis, associated with lower mortality. However, serum IgG elevation was found in 67.7% of decompensated cirrhosis, and the two markers did not correlate with each other. Elevated IgG levels were universal in compensated cirrhosis, and mean IgG levels were lower in acute on chronic liver disease mortality cases, suggesting a correlation with the capacity to mount an immune response in compensated disease. Elevated IgG levels were associatedwith lower 90-day mortality, although not statistically significant. Cirrhosis with elevated IgG had a lower incidence of variceal bleeding, but further studies are needed regarding its correlation with portal hypertension. Contrary to expectations, elevated IgG patients did not have a lower incidence of infective complications like pneumonia, UTI, cellulitis, or spontaneous bacterial peritonitis (SBP), challenging the conventional correlation of IgG levels with protective immune response. Conclusion: Serum IgG levels emerge as a practical tool for predicting outcomes and assessing humoral immune capacity in cirrhosis. The study highlights the complex immune dysfunctions in cirrhosis, revealing the paradox of hypergammag lobulinemia coexisting with functional immunosuppression. Elevated IgG levels, especially in the presence of hypergammaglobulinemia, may confer a survival benefit in decompensated cirrhosis, challenging existing paradigms in cirrhosis management and offering insights for risk stratification and therapeutic considerations.

INTRODUCTION

Decompensated cirrhosis increases the susceptibility to recurrent infections and diminishes adequate response to vaccination [1]. Hypergammaglobulinemia (HGG) is common in cirrhosis, attributed to the endotoxemic state due to gut bacterial transmigration and it serves as an indicator of immune dynamics and the body's sustained ability to generate antibody responses.

Cirrhosis is an end-stage liver disease. In its compensated stage, it rarely causes clinical symptoms. However, as the disease progresses, disturbed blood flow through the liver leads to portal hypertension, resulting in complications such as ascites, variceal bleeding, and hepatic encephalopathy. Furthermore, some patients may progress to develop hepatocellular carcinoma (HCC).

Decompensated liver cirrhosis induces functional immunosuppression, characterized by an increased

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susceptibility to infections and a failure to mount protective immune responses to prophylactic vaccinations. Interestingly, despite functional immunosuppression, cirrhotic patients often exhibit hypergammaglobulinemia (HGG), seemingly contradicting their poor ability to develop vaccine-induced antibodies.

Follicular T helper (Tfh) cells play a central role in humoral immunity by aiding B cells and enabling their maturation into antibody-producing plasma cells. Cirrhosis-associated immune dysfunctions (CAID) in adaptive immunity result from dysregulation at the Tfh level, contributing to the inability of patients with advanced cirrhosis to mount protective antibody responses despite concurrent HGG [2-4].

The role of Serum IgG levels, a cost-effective and readily available test, in predicting outcomes in cirrhosis and assessing humoral immune capacity, has been inadequately studied, with limited research available on this aspect.

MATERIALS AND METHODS

This prospective study enrolled 100 consecutive cirrhotic patients admitted to our hospital between April 2022 and December 2023, encompassing cases of compensated cirrhosis, decompensated cirrhosis, and acute-on-chronic liver disease. Exclusions comprised individuals under 18 years, moribund patients, and those with cirrhosis due to Autoimmune Hepatitis. Consent was obtained or waived by all participants in this study. The study was approved by the Institutional Ethics Committee of Madurai Medical College, Madurai, (Institutional Ethics Committee of Madurai Medical College, Madurai issued approval CDSCO: Reg No. ECR /1365/Inst/TN/2020& DHR Reg.No.EC /NEW/ INST/ 2022/ 0059) and performed as per the standards laid down by the Declaration of Helsinki for medical research involving human subjects.

Baseline characteristics, including age, sex, presenting symptoms, etiology, and laboratory workup, were recorded. Patient management followed standard treatment protocols based on presentation. Serum IgG levels were measured using a standardized operating protocol. Patients were prospectively followed for 12 months, and the correlation between serum IgG levels and prognostic outcomes was assessed, including 90- day and overall mortality rates. The development of complications such as Hepatorenal syndrome, Upper gastrointestinal bleeding, and infective complications like Pneumonia, Urinary tract infections, Cellulitis, and Spontaneous bacterial peritonitis were recorded during the follow-up period.

The mean Serum IgG level of the study population and, its variations with state of liver disease (compensated, decompensated, and acute-on-chronic liver failure) were evaluated. Serum IgG levels correlated with the severity of liver disease based on MELD and CHILD scores were evaluated. Hypergammaglobulinemia and IgG level correlation as a marker of immune response in cirrhosis was evaluated by follow-up of the study population.

The study also evaluated the correlation of IgG levels with overall and 90-day mortality. Furthermore, differences in outcomes and disease characteristics were assessed between cirrhosis patients with elevated IgG levels (>16 g/l) and normal IgG levels (< 16 g/l). Hypergammaglobulinemia and IgG level correlations were explored as markers of immune response in cirrhosis.

This study provides a comprehensive analysis of Serum IgG levels in a diverse cirrhotic population, offering valuable insights into the relationship between immunological parameters and disease outcomes. The findings contribute to the evolving understanding of cirrhosis management and underscore the potential clinical relevance of Serum IgG levels as prognostic indicators.

Serum IgG methodology

After patient enrollment, 2 ml blood samples were collected between 8 am and 10 am. The samples were drawn into prechilled red tubes, immediately placed on ice, and then transferred to the multidisciplinary research unit at Madurai Medical College, Government Rajaji Hospital. Subsequent centrifugation at 4°C facilitated serum separation, then stored at -80 °C. Serum Human Total Immunoglobulin G (IgG) was assessed using an enzyme-linked immunosorbent assay (ELISA) with the Human IgG Total Uncoated ELISA Kit (Invitrogen by Thermo Fisher Scientific, cat no 88-50550). The kit contains the necessary reagents, standards, buffers, and diluents for quantitative ELISA. Following the manufacturer's instructions, the IgG ELISA was performed to accurately measure human IgG total protein levels in serum samples from patients with chronic liver diseases, with a detection range between 1.6-100 ng/mL. This standardized methodology ensures precise evaluation of serum IgG levels in the study cohort.

Statistical analysis was conducted using SPSS version 20. Independent variables were analyzed with the One-way ANOVA test, and paired group comparisons utilized the Wilcoxon matched-pairs signed rank test. Overall survival was assessed using Kaplan-Meier estimates. Cross-table analysis was performed, and significance was evaluated with the Chi-square and Fisher's exact tests. Differences in survival were analyzed using log-rank tests. A p-value < 0.05 was deemed statistically significant, denoted as follows: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.00$

RESULTS

This prospective study enrolled 100 cirrhotic patients, comprising 82 (82.01%) with decompensated cirrhosis, 10 (11.24%) with compensated cirrhosis, and 8 (6.75%) with acute-on-chronic liver disease. The mean age was 49.01 years, with a male predominance (88%), and ethanol-related cirrhosis was prevalent in 73% of cases. (Fig.1)

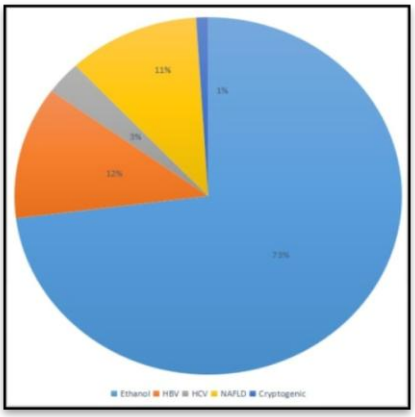

Fig.1 Etiology of study population ; Majority were ethanol related cirrhosis(73%) followed by 12 % were Hepatitis B related cirrhosis , 11% were NAFLD related cirrhosis, 3 % were Hepatitis C related cirrhosis and 1% was Cryptogenic Cirrhosis

Normal serum IgG levels range from 6 to 16 g/L. In our study, the mean IgG level was 20.80 g/L, with compensated cirrhosis exhibiting a higher mean IgG level (22.67 g/L) than decompensated cirrhosis (20.17 g/L) (Fig.2) (Table 1). However, no statistically significant difference was observed between the groups (p-value 0.463). Elevated IgG levels (>16 g/L) were present in 69% of the cohort, with statistical significance noted in decompensated and compensated cirrhosis (p-value 0.031). Among 11 patients with low IgG levels (<6 g/L), 4 deaths were reported, primarily in decompensated cirrhosis and Acute-on-Chronic Liver Failure (ACLF).

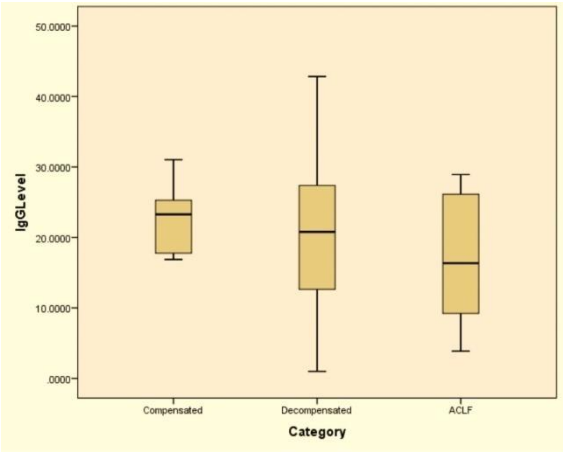

Fig. 2 IgG level of study population; Distribution of Serum IgG level in Compensated cirrhosis, Decompensated cirrhosis and Acute on chronic liver failure.

Table 1 Mean IgG level of study population

IgG level of study population	Mean IgG level (Mean ±SD)	Fold above normal range (Normal range:6-16 g/l)
ACLF	17.03±9.6857158	1.06
Compensated	22.67±4.9871290	1.41
Decompensated	20.17±9.9127910	1.26

No statistically significant difference was observed in mean IgG levels regarding the severity of liver disease, as assessed by the CHILD score or MELD score (Tables 2 and 3).
MELD score (Tables 2 and 3).

Table 2 IgG level and CHILD score

Child score	N	% of total	(mean ±sd)	median	mode
A	12	10.73%	18.04±7.24	17.83	4.17
B	32	33.02%	20.82±11.26	22.21	1.00
C	56	56.25%	20.26±8.95	20.79	20.54

Table 3 IgG level and MELD score

MELD Score	N	% of Total	(Mean ±SD)	Median	Mode
MELD <17	50	47.63%	19.22±9.37	20.54	20.54
MELD > 17	50	52.37%	21.13±9.68	22.36	3.86

The mortality rate was 39.63% (39 patients), with no significant difference in mean IgG levels between the mortality and survival groups. (Fig.3). However, in ACLF, the mortality group had a significantly lower mean IgG level (12.53 g/L) than decompensated patients (21.95 g/L, p-value 0.0386).

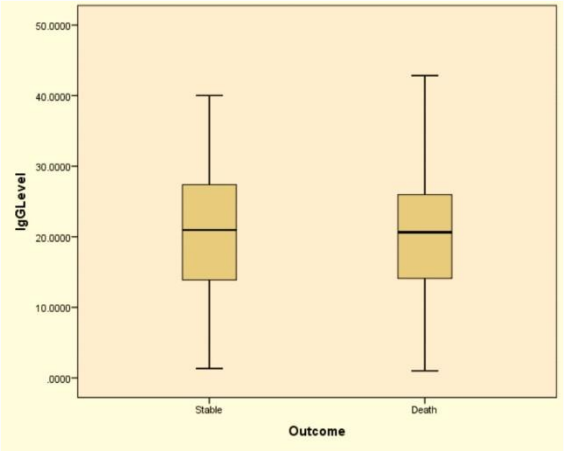

Fig. 3 IgG level distribution in mortality and survival groups; No significant difference in mean IgG level between mortality and survival group

Elevated IgG levels in decompensated cirrhosis corresponded to a reduced survival rate of 56.36%, though without statistical significance (p-value 0.1111). (Fig. 4, Table 4).

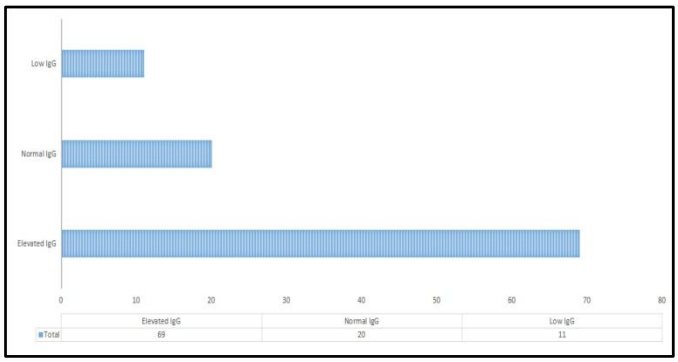

Fig. 4 Distribution of study population based on IgG level; Low < 6g/l, Normal 6-16g/l and Elevated > 16g/l

Table 4 Elevated IgG Level – Compensated versus Decompensated cirrhosis

IgGLevel	Compensated	Decompensated	Total	p-value
Normal IgG <16 g/l	0	27	27	0.031
Elevated IgG >16 g/l	10	55	65	
Total	10	82	92	

In the entire cohort, cirrhosis with elevated IgG was associated with a lower 90-day mortality (23%) compared to normal IgG levels (25%), but this lacked statistical significance (p-value 0.4125). Similarly, no significant difference was observed in 90-day mortality between decompensated cirrhosis patients with elevated and normal IgG levels (p-value 0.092).

Comparing cirrhosis patients with elevated and normal IgG levels, elevated IgG demonstrated a lower incidence of upper gastrointestinal bleeding (p-value 0.01409). Other parameters, including infective complications, hepatorenal syndrome

(HRS), hypergammaglobulinemia, and coagulopathy, showed no significant differences between the two groups. (Table 5).

Table 5 Correlation between elevated and normal IgG levelswith complications, Mortality, and paramount parameters.

Parameter	Elevated IgGn(%) (69 patients)	Normal IgG n(%) (31 patients)	P value
UGI bleed	26 (37.68%)	19 (61.2%)	0.01409(Chi square test)
Infective complications	15 (21.7%)	7 (22.5%)	0.4626(Chi square test)
HRS	6 (0.08%)	2 (0.06%)	0.5242(Fisher extract test)
Coagulopathy	31 (44.9%)	15 (48.3%)	0.3741(Chi square test)
Thrombocytopenia	53 (76.8%)	27 (87%)	0.1175(Chi square test)
MELD >17	34 (49.2%)	16 (51.6%)	0.4144(Chi square test)
HGG	25 (36.2%)	10 (32.2%)	0.35(Chi square test)
90 day mortality	15 (21.7%)	8 (25.8%)	0.2341(Fisher extract test)
Overall mortality	28 (40.5%)	11 (35.4%)	0.629(Chi square test)

UGI Bleed-Upper gastrointestinal bleed; HRS- Hepatorenal syndrome; HGG – Hypergammaglobulinemia

In decompensated cirrhosis, 36.58% exhibited hypergammaglobulinemia (globulin level > 3.5g/L), associated with a higher survival rate of 63.33%, and significantly lower mortality (36.67%) than those with normal globulin levels (p-value 0.024). (Table 6). Decompensated cirrhosis with both hypergammaglobulinemia and elevated IgG levels had no significant difference in mortality compared to those with normal globulin levels (p-value 0.9270). These findings underscore the complexity of cirrhosis outcomes, suggesting potential implications for risk stratification and therapeutic considerations.

Table 6 Hypergammaglobulinemia and outcome.

Globulin level	outcome		Total	P value
	Death	Stable		
Hypergammaglobulinemia	14	21	35	0.024
Normal globulin	25	40	65	
Total	39	61	100	

DISCUSSION

The liver serves as a filtration barrier and first line of defence, crucial for innate immunity, effectively segregating pathogens and toxins from the gut and preventing their entry into the systemic circulation [5].

In liver cirrhosis, several alterations occur, affecting both the liver and gastrointestinal tract, culminating in immune activation. Primarily, compromised hepatic function hinders the effective management of gut-derived antigens and endotoxins due to defective Kupffer cell function [6]. This results in the activation of extrahepatic antibody-producing sites. Simultaneously, structural alterations in the intestinal mucosa facilitate the translocation of bacterial products, especially lipopolysaccharide (LPS), into the bloodstream [7]. Collateral circulation, secondary to portal hypertension, establishes a direct route for gut antigens and endotoxins to reach antibody-producing cells.

LPS, a predominant pathogen-associated molecular pattern (PAMP), recognized by Toll-like receptors, plays a pivotal role in the pathogenesis of the liver disease. With over 80% of the body's macrophages, particularly Kupffer cells, the liver efficiently handles antigens like LPS from the portal vein, aiding in bacterial clearance. The liver maintains low mRNA levels of Toll-like receptors (TLRs) and signaling molecules compared to other organs, suggesting heightened tolerance to TLR ligands from the gut microbiota. Kupffer cells, expressing TLR4, respond to gut-derived toxins, coordinating inflammatory responses, and exhibiting tolerance [8].

Various cells, including hepatocytes, hepatic stellate cells, sinusoidal cells, and biliary epithelial cells, express TLR4, contributing to toxin processing and mounting immune responses. A breach in this tolerance during liver injury, especially chronic liver disease, results in immune activation through TLR downstream pathways, precipitating robust inflammatory reactions. This includes downstream activation of nuclear factor kappa B (NF-κB), mitogen-activated protein (MAP) kinases, interferon releasing factor -3 (IRF-3), and transcription of various inflammatory cytokines, chemokines, and antimicrobial genes, potentially contributing to the progression of liver disease [8].

TLR family members play distinct roles in stimulating the immune response. TLR-2 recognizes cell wall components of gram-positive bacteria, while TLR-4 is stimulated by bacterial DNA, lipoproteins, and heat shock protein-60. TLR-7 activates memory B cells, further illuminating the intricate pathways of immunoglobulin synthesis [9-11].

Previous studies provide evidence for augmented serum immunoglobulin synthesis induced by liver dysfunction, responding to shifts in bacterial microflora and bacterial translocation. The consequent Hypergammaglobulinemia (HGG) in liver cirrhosis arises from elevated gut-derived endotoxins resulting from portosystemic shunting.

Hypergammaglobulinemia (HGG) in liver cirrhosis is likely a response to increased gut-derived endotoxins due to portosystemic shunting. Contrary to the assumption that HGG reflects elevated systemic endotoxin levels, Basho *et al*. demonstrated that HGG identifies individuals with a more intact ability to produce IgG antibodies, indicating a preserved immune system and a favorable prognosis. Patients with decompensated cirrhosis and HGG (IgG >16g/L) exhibited improved survival compared to those with IgG values within normal ranges [12].

Chronic liver diseases (CLD), particularly decompensated cirrhosis, are characterized by abnormal immunological responses, including autoantibodies and hypergammaglo bulinemia. While hypergammaglobulinemia has been considered a marker for histologically advanced fibrosis, its role in disease progression remains complex. Our findings

align with the observation that hypergammaglobulinemia may indicate a protective response, showcasing the body's capacity to mount an immune response. In the context of CLD, hypergammaglobulinemia may represent a paradox, serving as both a marker of protection and an indicator of disease advancement.

The evaluation of IgG, a marker of adaptive immune response, is limited in existing studies. Our study addresses this gap by exploring the predictive role of serum IgG levels in assessing the prognosis of cirrhosis.

The cost-effectiveness and ready availability of the IgG test make it a practical tool for clinical use. Comparing our results with previous studies, including Fallatah *et al*., [13] discrepancies in the prevalence of hypergammaglobulinemia alongside elevated serum IgG levels are evident. Unlike some observations, our study finds that elevated IgG levels were not consistently related to the severity of liver disease. Notably, elevated IgG was universal in all compensated cirrhosis patients in our study, challenging previous observations.

Contrary to expectations, decompensated cirrhosis patients with hypergammaglobulinemia exhibited a superior survival rate in our study. This challenges previous studies linking hypergammaglobulinemia to adverse outcomes. The potential protective role of hypergammaglobulinemia in decompensated cirrhosis requires further exploration.

Studies by Burton *et al* and Tergast *et al* proposed that hypergammaglobulinemia may signify an early stage of decompensation, with retained immune responsiveness. Our study aligns with this hypothesis, indicating a survival benefit associated with hypergammaglobulinemia in decompensated cirrhosis [14, 15].

Importantly, current risk scores for patients with cirrhosis, such as the MELD (-Na) and Child-Pugh scores, include markers of liver and renal function, yet immunological markers are currently not considered in these models. However, our data and those presented by Tergast *et al*. emphasize that immunological markers may play an important role in prognostication in decompensated cirrhosis. In line with this concept, IgG may serve as an important marker to reflect immune competence and the preserved ability to mount IgG responses following systemic exposure to a surplus of gut-derived antigens in the context of bacterial translocation aggravated by portal hypertension.

In evaluating the optimal IgG cutoff, our study did not find significant differences in overall mortality or 90- day mortality when the cutoff was reduced to 11 g/L from the conventional 16g/L. This suggests that the conventional cutoff may remain valid in predicting outcomes.

The potential significance of IgG levels in patients with cirrhosis suggests a link between IgG reduction, immune impairment, and prognosis. It also introduces the idea of incorporating immunological markers, such as IgG, into existing risk scores for cirrhosis. The study by Basho *et al*.suggests a connection between higher serum IgG levels, specific Tfh cell functions, and reduced mortality risk in advanced cirrhosis. The consideration of IL-2 blockade as a therapeutic approach to prevent immunosuppression in cirrhosis is also discussed. The late occurrence of Tfh cell dysfunctions in the course of chronic liver disease and the predictive potential of increased IgG levels for preserved Tfh cell function are highlighted. Further studies are suggested to explore these connections and potential therapeutic interventions

In summary, our study explored serum IgG levels in cirrhosis patients and their association with disease severity and outcomes. The key findings include the mean serum IgG levels were 1.26-fold higher than normal in cirrhosis patients, but there was no correlation with the severity of liver disease according to MELD/CHILD score. Hypergammaglobulinemia was present in 36.58% of decompensated cirrhosis, and it was associated with lower mortality. Serum IgG elevation was found in 67.7% of decompensated cirrhosis, but the two markers (hypergammaglobulinemia and elevated IgG) did not necessarily correlate with each other. Elevated IgG levels were universal in compensated cirrhosis, and mean IgG levels were lower in acute on chronic liver disease mortality cases, suggesting a correlation with the capacity to mount an immune response in compensated disease. Elevated IgG levels were associated with lower 90-day mortality, although the association was not statistically significant. Cirrhosis patients with elevated IgG had a lower incidence of variceal bleeding, but additional studies are required to explore its correlation with portal hypertension.

Contrary to expectations, patients with elevated IgG did not exhibit a lower incidence of infective complications such as pneumonia, urinary tract infections (UTI), cellulitis, or spontaneous bacterial peritonitis (SBP), challenging the conventional correlation of IgG levels with a protective immune response. These findings provide valuable insights into the complex relationship between IgG levels and various aspects of cirrhosis, suggesting potential implications for prognosis and disease management. Further research is recommended to elucidate the underlying mechanisms and confirm these associations.

Limitations of study

Since the majority of the study population was decompensated cirrhosis comparison with stable compensated cirrhosis was not feasible due to the low number in compensated cirrhosis. Follicular T Helper cells play a major role in mounting immune response by stimulating B cells and secreting IgG, IL-2 assay as a marker of Follicular T Helper cells was not done in our study. Serum half-life of IgG is 26 days. It is tempting to assume that after some time patients with previous HGG could progress in their immune impairment, leading to higher mortality in the long term. Unfortunately, we did not access IgG levels over time. It is tempting to estimate that IgG reduction could be associated with a worsening prognosis. Hence, future studies might investigate the potential value of repeated IgG measurements.

CONCLUSIONS

Serum IgG levels emerge as a practical tool for predicting outcomes and assessing humoral immune capacity in cirrhosis. The study highlights the complex immune dysfunctions in cirrhosis, revealing the paradox ofhypergammaglobulinemia coexisting with functional immunosuppression. Elevated IgG levels, especially in the presence of hypergammaglobulinemia, may confer a survival benefit in decompensated cirrhosis, challenging existing paradigms in cirrhosis management and offering insights for risk stratification and therapeutic considerations. Further studies are warranted to explore the

correlation of elevated IgG with portal hypertension and its implications for cirrhosis outcomes

DISCLOSURES

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee of Madurai Medical College, Madurai issued approval CDSCO: Reg.No.ECR/1365/Inst/TN/2020&DHR Reg.No.EC/NEW/IN ST/2022/0059. The study was approved by the Institutional Ethics Committee of Madurai Medical College, Madurai, and performed as per the standards laid down by the Declaration of Helsinki for medical research involving human subjects. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: Funding: The study project was funded by the Department of Health Research, Ministry of Health and Family Welfare, Government of India through MRU, Madurai Medical College (No. V25011/464/2015/HR).

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgment

We acknowledge our Dean, Nodal officer of the Multi-Disciplinary Research Unit at, Madurai Medical College, Madurai, Tamil Nadu, India under Department of Health Research, Government of India, for the support of this study. And also acknowledge and thank Mrs. K. Vennila and B.Punithavathi lab technicians for processing the samples.

Funding

The study project was funded by the Department of Health Research, Ministry of Health and Family Welfare, Government of India through MRU, Madurai Medical College (No. V25011/464/2015/HR)

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How to cite this article:

Vijai Shankar Chidambara Manivasagam, Vinoth Sermadurai, Kannan Mariappan, Ramani Rathnavel, Ramajayam Govindan, Mahesh Kumar, Sriram P. B., Subburathinam Gopalan and Kishwanth Rayappan**.** (2024). Role of serum igg as a prognostic marker in chronic liver disease in a tertiary care centre. *International Journal of Current Advanced Research.*13(04), pp.2895-2900.