Recommendations for Hepatitis B Immunoglobulin and Antiviral Prophylaxis Against Hepatitis B Recurrence After Liver Transplantation

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Cite this article as: Akarsu M, Onem S, Turan I, et al. Recommendations for hepatitis B immunoglobulin and antiviral prophylaxis against hepatitis B recurrence after liver transplantation. *Turk J Gastroenterol.* 2021; 32(9): 712-719.

ABSTRACT

The combination of hepatitis B immunoglobulin and potent nucleos(t)ide analogs after liver transplantation is considered as the standard of care for prophylaxis against hepatitis B virus recurrence. However, the recommended doses, route of administration, and duration of HBIG administration remain unclear. Moreover, hepatitis B immunoglobulin-free prophylaxis with potent nucleos(t)ide analogs has shown promising disease outcomes in preventing hepatitis B virus recurrence. The current recommendations, produced by the Turkish Association for the Study of the Liver, Acute Liver Failure and Liver Transplantation Special Interest Group, suggest a reduced need for hepatitis B immunoglobulin administration with effective long-term suppression of hepatitis B virus replication using potent nucleos(t)ide analogs after liver transplantation.

Keywords: *Hepatitis B, liver transplantation, recurrence*

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most important causes of chronic liver disease and remains a major cause of liver-related morbidity and mortality worldwide.[1] In Turkey, despite a successful HBV vaccination program and efforts to reduce transmission and prevention, HBV infection remains a major public health problem, especially in the adult population. In 2009, an epidemiologic study of the adult population in the country determined hepatitis B surface antigen (HBsAg) positivity to be around 4% and hepatitis B core antibody (anti-HBc) positivity to be 31% in Turkey.[2]

Hepatitis B virus infection has a wide range of clinical consequences, including acute HBV infection, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Hepatitis B virus infection is present in approximately 50% of the patients with HCC, most of whom also have cirrhosis. Hepatitis B virus-related end-stage liver disease with or without HCC accounts for approximately 40-50% liver transplantation (LT) cases.[1]

Posttransplant HBV recurrence may lead to graft loss and mortality as a result of HBV-induced aggressive hepatitis. Before the introduction of hepatitis B immunoglobulin

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Received: ***July 26, 2021*** *Accepted:* ***August 31, 2021*** *Available Online Date:* ***September 20, 2021***
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DOI: 10.5152/tjg.2021.21608

(HBIG), patients with HBV-related cirrhosis were not suitable candidates for LT due to high rates of posttransplant HBV recurrence, which resulted in low graft and patient survival rates.[3,4] After the advent of HBIG monotherapy, the risk of HBV recurrence after LT was reduced, and the overall survival rate was improved.[3,4] Before the introduction of nucleos(t)ide analogs (NAs), HBIG in high doses was used as monoprophylaxis to prevent HBV recurrence after LT. In the early years after the introduction of NAs, lamivudine (LMV), adefovir dipivoxil (ADV), or combinations of thereof with HBIG were used for the prevention of HBV recurrence after LT.[3,4] Lamivudine and ADV are no longer recommended as optimal first-line prophylactic therapies due to their weak potencies and the high rates of resistance development. Potent NAs such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) combined with HBIG are effective in preventing HBV recurrence after LT and are well tolerable.[3,4] These combination treatments have dramatically reduced the HBV recurrence rates and improved the clinical outcomes after LT.[3,4] There are very limited data on the use of tenofovir alafenamide (TAF) in transplant settings.

Hepatitis B immunoglobulin is prepared by cold ethanol fraction of pooled human plasma that contains high titers of hepatitis B surface antibody (anti-HBs). It has a polyclonal IgG structure antibody against HBV, and its IgG subgroup distribution is highly proportional to human plasma.[4-6] The mechanism of action of HBIG is not very well known. Hepatitis B immunoglobulin neutralizes HBV virions in circulation, promotes the lysis of infected hepatocytes by the antibody-dependent cellular toxicity, possibly prevents native hepatocyte infection by forming immune complexes with circulating HBV particles, and blocks the HBV receptor in hepatocytes.[4-6] The half-life of HBIG is approximately 22 days.[5] Disadvantages of HBIG include its high cost and parenteral administration, the need for lifelong treatment, and the possibility of mutation at the HBV surface gene's "a" determinant region.[6]

The HBIG doses, routes of administration, and administration frequencies and durations after LT are heterogenous among transplant centers. No HBIG administration protocol is available. The recommendations published herein were prepared by a study group of expert physicians based on the domestic and international literature and aim to prevent HBV recurrence after LT with respect to the recommendations of physicians who are interested in the subject according to the national and international literature. The specific aims are as follows:

(a) to offer recommendations to gastroenterologists and transplant surgeons regarding HBIG doses, routes of administration, and administration frequencies and durations during and after LT,
(b) to prevent unnecessary HBIG administration and the associated outpatient clinic admissions, and
(c) to prevent adverse effects due to HBIG administration.

METHODS

To establish the recommendations, a study group of experienced gastroenterologists and LT surgeons was formed. The most common problems associated with HBIG use during and after LT were determined. In groups of 2, using search terms from previously formulated questions, a systematic literature research was conducted using the patient, intervention, comparison, outcome method. Draft recommendations were prepared according to the identified articles and presented to the study group. The draft recommendations related to each question were discussed, and the final recommendations were produced based on consensus. The evidence and recommendations were graded according to the U.S. Preventive Services Task Force recommendations.[7] The grades to qualify the overall evidence for a service was graded on a 3-point scale (good, fair, or poor). The recommendations are listed in order from strongest to weakest[7] (Tables 1 and 2). The average agreement of the participants (the experts) was graded based on the Adherence Patterns and Behaviors Questionnaire (from Strongly Disagree as 0% to Strongly Agree as 100%).

What Are the Risk Factors for HBV Recurrence After LT?

Hepatitis B virus recurrence after LT is defined as HBsAg positivity and/or detectable levels of HBV DNA, which

Table 1. Evidence Power Classification

Level I, Category A	Prospective, randomized comparative clinical study, and meta-analyses
Level II, Category B	Planned, non-randomized prospective, retrospective, and cohort studies
Level III, Category C	Uncontrolled, experience, phenomenon presentation, or expert opinions

Table 2. Suggestion Power Classification

A	Certainly effective
B	Seems effective
C	Somewhere between side effects and effectiveness
D	Seems ineffective
E	Seems hazardous

also pose a risk of graft loss.[3,4,8-10] Several risk factors for HBV recurrence after LT have been identified. Hepatitis B "e" antigen (HBeAg) positivity and detectable serum HBV DNA levels prior to LT are important risk factors.[3,4,8-11] Other risk factors are concomitant hepatitis D virus (HDV) infection or human immunodeficiency virus (HIV) infection, HCC prior to LT, low compliance with antiviral treatment, and antiviral drug resistance.[3,4,8,11-14] Hepatitis D virus coinfection does not increase the risk of HBV recurrence after transplantation; in fact, it reduces it. However, in the case of recurrence, the patient's clinical course is severely affected, and the prognosis is poor.[12-14] The prophylactic use of weak antivirals, such as LMV, ADV, and telbivudine, is also considered to pose a high risk of HBV recurrence.[1,12,13]

The presence of HCC prior to LT has been associated with HBV recurrence after LT.[13,14] In a study of including 296 patients who had LT due to HBV, and were followed up for 46 months, 8 patients developed HBV recurrence, 7 of whom had HCC prior to LT. The study reported that patients with HCC prior to LT had a hazard ratio of 12.26 (CI: 1.487-101.086, P = .02) for HBV recurrence when compared to those without HCC.[15]

Recommendation: *Patients who are serum HBV DNA positive prior to LT, are HBeAg positive, have HCC, have HDV or HIV coinfection, are antiviral drug-resistant, have low compliance with antiviral treatment, and are at a high risk of HBV recurrence (Evidence Level I, grade of recommendation A).* The average agreement of the participants was 100%.

What Is the Recommended Dose of HBIG Administration During the Anhepatic Phase and the Early Period After LT?

Hepatitis B immunoglobulin administration is planned in 3 phases: anhepatic phase, first 7 days after LT, and long-term maintenance treatment. Hepatitis B immunoglobulin becomes bioactive quickly and disperses to plasma and extracellular liquids after intravenous (IV) administration. Owing to its full and quick bioavailability, it reaches a steady state in intra- and extracellular compartments in 3-5 days.[5,6,16] In the early phase after LT, HBIG kinetics differ among the patients. Serum HBIG concentrations may decrease due to bleeding, blood and blood products transfusions during LT.[6,16]

Several protocols of HBIG doses and treatment duration in the anhepatic phase and early phase after LT have been used in transplant centers. Before the introduction of NAs, HBIG was administered intravenously in high doses (10 000 IU) in the anhepatic phase, and daily during the first week, followed by weekly and then monthly administration in fixed doses with a target to approach 500 IU/L.[4,9,17] Hepatitis B immunoglobulin administration needs to be monitored according to the anti-HBs titer and maintained at >100 IU/L.[4,18-20] Dose reductions have been tested. In a previous study, 2000 IU/day of HBIG per day was administered intravenously during the first week after LT and then additional doses were used when anti-HBs titers dropped below 100 IU/L.[18]

Because of the high cost of HBIG infusions in large doses, their adverse effects, and the need for frequent hospitalization, many studies have investigated the efficacy of combinations of low-dose HBIG with NAs. Intramuscular (IM) administration of low-dose (400-800 IU) HBIG combined with an NA has been reported to produce favorable outcomes.[19,21-23] In a multicenter trial, the HBV recurrence rate decreased to 1% in the first year and 4% by the fifth year, at a cost of less than 10% of the cost of high-dose administration.[19] Studies in Turkey have reported similar results.[20,24] Moreover, a meta-analysis of 11 studies (303 patients) found an overall HBV recurrence rate of 1% when TDF or ETV was used in combination with HIBG.[25] In the reviewed studies, HBIG was administered in doses ranging between 5000 and 10 000 IU during the anhepatic phase and between 400 and 2000 IU per day during the first week after LT.[25] Therefore, low-dose IM administration of HBIG in combination with a potent NA is an effective prophylactic option for preventing HBV recurrence.

Recommendation: *To prevent HBV recurrence, during the anhepatic phase, 5000 IU of HBIG should be administered intravenously to low-risk patients and 10 000 IU should be administered to high-risk patients. During the first 7 days after LT, HBIG administration should be continued with maximum daily doses of 2000 IU, until HBsAg seroconversion. After the seventh day, HBsAg and anti-HBs titers should be tested, and if HBsAg is still positive, 2000 IU per day should be administered for an additional 7 days (Evidence Level II, grade of recommendation B).* The average agreement of the participants was 94%.

What Is the Target Anti-HBs Titer During HBIG Maintenance Treatment?

After the introduction of potent NAs, it is not necessary to reach high levels of anti-HBs titers with HBIG-NA

combination. The HBIG dose and route of administration do not significantly affect the HBV recurrence rates in LT recipients treated with HBIG-NA combinations.[4,26] In contrast to immunosuppressive patients, in healthy individuals, anti-HBs titers of >10 IU/L after successful HBV vaccination are thought to be protective.[27]

The anti-HBs levels may differ according to the psttransplantation periods. Some studies have suggested that anti-HBs titers should be >500 IU/L 1-3 months after LT, >250 IU/L 6-12 months after LT, and >100 IU/L in the subsequent months.[4,28,29] Hepatitis B surface antibody titers may also differ between patients or even in the same patient receiving treatment on a regular basis.

Previous studies have also evaluated the efficacy of subcutaneous (SC) HBIG administration. In one study, HBIG was subcutaneously administered to LT recipients for more than 12 months to reach target anti-HBs titers of >150 IU/L. After 48 weeks, the mean anti-HBs titer was 232 IU/L, and no recurrence was observed.[30] In another study of 176 patients receiving a combination of HBIG and a potent oral NAs, anti-HBs titers were maintained at 100-250 IU/L. Only 2 patients were HBsAg positive after a mean follow-up of 43 months, 1 of whom did not use the NA regularly.[31] Another study used an HBIG-ETV combination to reach a target anti-HBs titer of 500 IU/L in the first 6 months and maintain it at >100 IU/L thereafter. No HBV recurrence was observed after a mean follow-up of 25 months.[32] In our experts' opinion, the target serum anti-HBs level should be above 50 IU/L during the maintenance period of HBIG administration.

Recommendation: *The maintenance HBIG should be administrated in doses of 2000 IU monthly, and anti-HBs titers should be maintained above 50 IU/L. If the anti-HBs titer is more than 200 IU/L, the HBIG dose should be skipped (Evidence Level II, grade of recommendation A).* The average agreement of the participants was 92%.

Routes of HBIG Administration

Hepatitis B immunoglobulin may be administered via the IV, IM, or SC route. The anti-HBs titer and HBIG half-life did not differ between administration routes.[33] When HBIG is administered intramuscularly, it is slowly secreted into the vascular system and continuously via the lymphatics and reaches its maximum concentration at 2-4 days. The bioavailability of HBIG administrated via the SC and IM routes is comparable to that of HBIG administered via the IV route. A study comparing the pharmacokinetics of IV and IM administrations found no significant differences in HBIG half-life (25.5 and 24.7 days, respectively), and mean anti-HBs titer at 2, 4, and 6 weeks (IV: 480, 319, and 221 IU/L, respectively; IM: 457, 310, and 218 IU/L, respectively).[33] Moreover, a review found no association between the HBIG administration route and HBV recurrence after LT.[34] Nevertheless, previous studies have reported conflicting results concerning the efficacy of different routes of administration.[30,35-37] However, these studies were limited by short follow-ups and small sample sizes. It should also be noted that different HBIG preparations may result in different antibody concentrations.

Hepatitis B immunoglobulin IM and SC administrations seem to be safe and effective in maintaining adequate anti-HBs levels.[4,26,33] These routes offer the benefit of easy administration outside the hospital. Some adverse effects, such as pain at the injection site and bleeding or bruises in patients with coagulopathy, may be seen. Switching from IV HBIG to IM and especially SC HBIG significantly improves the quality of life by reducing the frequency of side effects and increasing patients' autonomy.

Recommendation: *Hepatitis B immunoglobulin may be administered intravenously, intramuscularly, or subcutaneously. The route should be decided based on product availability and cost and should be discussed with the patient (Evidence Level II, grade of recommendation A).* The average agreement of the participants was 96%.

Is HBIG Monotherapy Appropriate to Prevent HBV Recurrence After LT?

Hepatitis B immunoglobulin administration is one of the most important milestones for preventing HBV recurrence after LT. Hepatitis B immunoglobulin monotherapy has reduced the HBV recurrence risk by about 70%.[3,4] The success rates increased further after the introduction of NAs. Studies have reported that HBIG and LMV combination treatment is superior to HBIG monotherapy.[4,34,38-42] With the advent of new NAs with high genetic barriers, the superiority of HBIG-NA combinations to HBIG monotherapy has become even more obvious. Studies have shown that HBV recurrence is associated with the doses of HBIG combined with LMV, whereas it is not associated with the doses of HBIG combined with TDF or ETV[25,34] The combination of HBIG and with potent NAs such as ETV and TDF is currently the standard HBV prophylactic approach after LT.[3,4] Such combinations improve the clinical end points and reduce HBIG doses and costs.

Recommendation: *Hepatitis B immunoglobulin monotherapy is not effective in preventing HBV reinfection in the posttransplant period and is therefore not recommended (Evidence Level I, grade of recommendation A).* The average agreement of the participants was 100%.

How to Manage Patients Who Do not Achieve HBsAg Seroconversion Despite 14-Day HBIG Administration After LT?

Hepatitis B virus recurrence is thought to be secondary to low anti-HBs titers due to extrahepatic sources of HBV or escape mutations in patients who were receiving HBIG.[43] Hepatitis B surface antigen should be evaluated after the administration of 2000 IU of HBIG per day for 7 days following LT. In the case of HBsAg positivity and/or anti-HBs titer below 100 IU/L, 2000 IU per day can be administered for an additional week. If HBsAg positivity is still detected after this, HBIG administration should not be continued. In our experts' opinion, HBIG administration can be prolonged to 28 days in patients with HDV coinfection.

Recommendation: *The duration of HBIG administration may be prolonged if HBsAg seroconversion does not occur at 14 days after LT. However, if HBsAg seroconversion does not occur even after long-term HBIG administration, the administration should be discontinued (Evidence Level III, grade of recommendation B).* The average agreement of the participants was 93%.

Is HBIG-Free NA Monotherapy Appropriate to Prevent HBV Recurrence After LT?

Hepatitis B immunoglobulin-free prophylaxis against HBV started with LMV. However, HBV recurrence was significantly high (35-50% of the patients) 2 years after LT.[44] After the introduction of potent NAs, this approach may be more feasible. Entecavir and TDF monotherapies are associated with significantly higher rate of HBV suppression compared to NAs with low genetic barriers.[1,3,4] A study of 265 HBV-infected LT recipients on ETV monoprophylaxis reported an HBsAg seroclearance rate of 92% and an undetectable HBV DNA rate of 100% 9 years after LT, suggesting that NA monotherapy could prevent HBV recurrence in LT recipients.[45] However, a systematic review found that LT recipients on ETV or TDF monoprophylaxis experienced HBV recurrence significantly more frequently than those on HBIG-NA combinations when HBV recurrence was defined according to HBsAg positivity (26% vs. 6%, $P < .001$).[25] The effect of HBsAg positivity on the long-term graft and patient survival is not well known.

Recommendation: *Nucleos(t)ide analogs monoprophylaxis without HBIG administration is not recommended in the early periods following LT (Evidence Level III, grade of recommendation A).* The average agreement of the participants was 96%.

When Should HBIG Administration Be Discontinued?

Studies on HBIG treatment discontinuation after LT are of interest, considering the cost and adverse effects of long-term administration. Studies have suggested that a combination of low-dose HBIG administration and potent NAs followed by NA monoprophylaxis is a reasonable and cost-effective approach, especially for patients with a low risk of HBV recurrence.[4,25,46] However, for patients with HCC or detectable HBV DNA levels prior to LT and patients with HDV or HIV coinfection, a decision for HBIG withdrawal should be made with great caution and after ensuring close monitoring.

Another point is when to discontinue HBIG administration after LT. Studies have shown that cessation is safe and feasible 1 year after LT in patients with a low risk of HBV recurrence.[4,46-48] According to a consensus report by the Spanish Association for the Study of the Liver, HBIG administration can be discontinued after 4 weeks in patients who have no risk factors for HBV recurrence, whereas it should be continued for up to 1 year in patients with detectable HBV DNA levels prior to LT.[49] According to the same report, it should be administered continuously to patients with HCC and HIV or HDV coinfection.[49] Lifelong HBIG administration is recommended for patients with a high risk of HBV recurrence and patients whose follow-up might be difficult for any reasons.[1,50]

Hepatitis B virus vaccination after LT has become an alternative approach. However, its efficacy is controversial, as the reported success rates range from 7% to 80%.[51] A lower response rate has been reported in LT recipients due to HBV-related cirrhosis than in patients with acute HBV liver failure (29% and 88%, respectively).[52] Furthermore, the long-term disease outcomes of HBV prophylaxis withdrawal after successful HBV vaccination are currently unknown.

Recommendation: *In low-risk patients, HBIG administration can be discontinued 1 year after LT, while potent NA*

treatment should be continued (Evidence Level III, grade of recommendation B). In high-risk patients, the combination of HBIG-NA treatment should be continued for a long-time to prevent HBV recurrence after LT (Evidence Level III, grade of recommendation A). The average agreement of the participants was 87%.

Can HBIG Treatment Be Discontinued in HBV Patients With HDV Coinfection?

Hepatitis B surface antigen positivity is necessary for HDV replication. Hepatitis B virus recurrence after LT in patients with HBV-HDV coinfection can lead to HDV recurrence with detrimental outcomes.[1,3,4,50] Currently, pegylated interferon is the only approved treatment approach for chronic HDV infection. However, the success rate of this treatment is quite low.[53] Moreover, interferon treatment after LT is associated with an increased allograft rejection risk. A previous study reported low rates of disease recurrence and better short- and long-term patient and graft survival with HBV-HDV coinfection than in patients with HBV mono-infection.[54] During the first days following LT, HBV and HDV exist in the circulation and infect hepatocytes. If HDV recurrence develops, the treatment options are limited, and the course of the disease is aggressive. For this reason, HBsAg negativity after LT is vital for preventing HDV recurrence.[53,54] To prevent HBV and HDV recurrence, a combination of long-term HBIG administration with an NA is recommended.[1,4,55] A retrospective study examining HBV-HDV coinfected LT patients receiving an HBIG-NA combination for 6 or 12 months reported HBV recurrence in the short-term treatment group.[52] The investigators suggested that even if HBV replication is controlled with potent NAs, the presence of HBsAg in serum may result in recurrence.[56] In a retrospective study in Turkey, no HDV recurrence was observed after a mean follow-up of 30 months in 128 LT patients with HDV receiving HBIG-NA combination treatment.[57] In another study, 13% of 104 LT patients with HDV receiving HBIG-NA combination treatment had HDV recurrence after a mean follow-up of 82 months.[58] In the literature, it has been reported that HBV DNA became negative on the fourth day with TAF and HBIG prophylaxis in transplantation from an HBV DNA-positive donor to an HDV-positive cirrhotic patient.[59] Since short-term HBIG administration after LT is associated with HBV/HDV recurrence and there is currently no effective treatment against HDV infection, a long-term HBIG-NA combination treatment is feasible and effective for these patients.

Recommendation: *To prevent HBV/HDV recurrence in patients with HBV-HDV coinfection, long-term HBIG administration combined with a potent NA is recommended (Evidence Level II, grade of recommendation A).* The average agreement of the participants was 94%.

What Is the Recommended Pophylaxis for LT Patients With HBV-HIV Coinfection?

Because HBV and HIV share common transmission routes, HBV-HIV coinfection can occur, although it has rarely been reported in Turkey. Low detectable HBV DNA levels may be seen during NA treatment. However, a study of 22 HBV-HIV coinfected patients receiving HBIG combined with an NA found no HBV recurrence after 3 and 5 years of follow-up.[60] The investigators reported that HBIG and antiviral combination was effective to prevent HBV reinfection.[60] Long-term HBIG administration is recommended because of the possibility of NA interruption or drug–drug interactions.[61]

Recommendation: *To prevent HBV recurrence in patients with HBV-HIV coinfection, long-term HBIG administration combined with an NA is recommended (Evidence Level II, grade of recommendation B).* The average agreement of the participants was 98%.

In summary, HBV-related acute liver failure and chronic liver failure are the most frequent indications for LT in Turkey. Prophylaxis against HBV recurrence is crucial for improving graft and patient survival. The current standard of care for the prevention of HBV recurrence after LT is HBIG combined with a potent NA, such as ETV or TDF. Hepatitis B immunoglobulin can be administered via the IV, SC, or IM routes, which should be determined on a case-by-case basis. The presence of HCC and HBV-HDV or HBV-HIV coinfection prior to LT is associated with posttransplant HBV recurrence. In these patients, the combination regimen should be administered for a long time after LT. Conversely, in patients with a low risk of HBV recurrence, such as patients with undetectable HBV DNA at LT, short-term HBIG administration and lifetime potent NAs seem to be effective in preventing HBV recurrence. Hepatitis B immunoglobulin administration should be personalized depending on the anti-HBs titers, with the goal of maintaining it above 50 IU/L.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

The data are not publicly available due to privacy or ethical restrictions.

Peer Review: Externally peer-reviewed.

Author Contributons: Concept – M.Akarsu, I.T., R.I., Z.K.; Design – M.Akarsu, I.T., Y.B., R.I., Z.K.; Supervision –I.T., M.Akdogan, M.Akyildiz, Y.B., R.I., Z.K.; Materials -; M.Akarsu, S.O., I.T.; Data Collection and/or Processing - ; M.Akarsu, S.O., I.T., G.A., M.Akdogan, M.Akyildiz, M.Aladag, Y.B., N.D., M.D., G.G., H.G., E.S., M.G., M.H., G.K., S.K., M.K., R.I., Z.K.; Analysis and/or Interpretation - ; M.Akarsu, I.T., R.I., Z.K.; Literature Search – M.Akarsu, S.O., I.T., G.A., M.Akdogan, M.Akyildiz, M.Aladag, Y.B., N.D., M.D., G.G., H.G., E.S., M.G., M.H., G.K., S.K., M.K., R.I., Z.K.; Writing – M.Akarsu, S.O., I.T., G.A., M.Akdogan, M.Akyildiz, M.Aladag, Y.B., N.D., M.D., G.G., H.G., E.S., M.G., M.H., G.K., S.K., M.K., R.I., Z.K.; Critical Reviews - M.Akarsu, I.T., Y.B., R.I., Z.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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