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ORIGINAL ARTICLE – OPEN ACCESS

Assessment of Post-transplantation Liver Function Tests in Patients Undergoing Allogeneic Stem Cell Transplantation

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ABSTRACT

Objective: Allogeneic hematopoietic stem cell transplantation is a treatment with a considerable rate of complete cure in hematological disorders. Hepatic complications are common causes of morbidity and mortality affecting the survival after stem cell transplantation. This study was conducted to identify risk factors for hepatic dysfunction and related potential factors affecting the survival in patients undergoing allogeneic hematopoietic stem cell transplantation.

Materials and Methods: We retrospectively evaluated the data from 300 allogeneic hematopoietic stem cell transplantation recipients between March 2004 and May 2014 in the Erciyes University Hematology and Bone Marrow Transplantation Center, Turkey. The study included 300 patients and their serial monitorization of the liver function tests, examined before and after transplantation.

Results: The transplantation in 30 patients was performed from haploidentical donors and in 13 patients from unrelated donors. We identified the liver function abnormalities in 71.7% of patients in the post-transplantation period. The most common causes were graft-versus-host disease (43.6%), drug toxicity (24.7%), and sepsis (13.9%). Post-transplantation liver abnormalities were more common in patients with acute leukemia ($p=0.02$), iron overload ($p<0.001$), and in those who also had transaminitis in the pretransplantation period ($p<0.001$). Relapsed underlying disease ($p<0.001$), iron overload, and a bilirubin level >2 mg/dL in association with hepatic dysfunction during the post-transplantation period were identified as major factors influencing mortality following transplantation ($p<0.001$).

Conclusion: We concluded that liver function abnormalities are frequent in the hematopoietic stem cell transplantation process. For a successful management, it is important to monitor the liver function and to identify additional risk factors before and after transplantation.

Keywords: Hematopoietic stem cell transplantation, liver function tests, hepatic dysfunction

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is successfully employed in hematological malignancies such as leukemia, lymphoma, or multiple myeloma, as well as in many disorders including some solid tumors, and immunodeficiency and genetic disorders. The HSCT has allowed marked control in disease and cure achievement. While long-term survival rates are very good in patients who were alive and disease free at least 2 years after HSCT (with 80% to 92% for 10 years), short-term survival rates range from 40% to 70% (1, 2). The loss of most of patients occurs within the first 2 years after transplantation as a result of relapse, graft-versus-host disease (GVHD), infections, and complications affecting major organs (3).

Hepatic complications are important due to a higher incidence as well increased mortality and morbidity (4). The transaminases including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are highly sensitive markers of the liver cell injury. AST is found in many tissues such as the liver, muscles, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes, while ALT is primarily produced in the cytosol of hepatic cells and therefore is a more specific indicator for the liver (5). These enzymes are routinely used to assess liver functions before and after transplantation in almost every clinic. In several series, the effects of hepatic complications on mortality and morbidity have been estimated as 4%–15% and 80%, respectively. The causes of hepatic injury include viral, bacterial, and fungal infections, drug toxicity, sinusoidal obstruction syndrome (SOS), GVHD, the disease relapse, and excessive iron deposition, among others. GVHD is the most common cause in patients undergoing allogeneic HSCT (4, 6). Several retrospective and prospective studies have shown risk factors for severe hepatic complications. Abnormal liver enzyme levels and pretransplantation hepatitis B (HBV) and hepatitis C (HCV) positivity are also well-defined risk factors. The sample size was limited in the majority of previous studies. This study was conducted on a relatively larger population to identify risk factors for hepatic dysfunction and potential factors influencing the survival in patients undergoing allogeneic HSCT.

MATERIALS and METHODS

In the present study, we retrospectively reviewed data from the HSCT recipients in the Erciyes University Hematology and Bone Marrow Transplantation Center between March, 2004 and May, 2014. The study included 300 patients who had adequate data in patient charts. Liver function tests were monitored for 1 year after transplantation, including ALT, AST, alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, and lactate dehydrogenase (LDH). In addition, the serum iron level, total iron binding capacity, ferritin level, and viral hepatitis markers (HbsAg and anti-HBS, anti-HCV, HBV DNA) were also assessed before and after transplantation. For the assessment of liver functions, values which were above the upper reference limit of our laboratory were considered for at least two consequent measurements. In patients with impaired liver functions, the time period for the onset of hepatic dysfunction was identified, and etiology was investigated. An onset of hepatic dysfunction was classified according to the time elapsed after transplantation: 0–30 days, 30–100 days, and after 100 day. This time classification is made to guide for etiology (Acute GVHD generally develops within the first 100 days after transplantation.) However, these periods are not used as a discriminative parameter.

Diagnostic Criteria

The Baltimore criteria were used for diagnosis in SOS. The SOS was diagnosed in the presence of hyperbilirubinemia (>2 mg/dL) along with two of following criteria: hepatomegaly, ascites, or unexplained weight gain >5% of the basal body weight. The discrimination of acute or chronic GVHD was made according to the National Institute of Health Consensus criteria (7). The diagnosis of hepatic GVHD was made using the clinical findings of GVHD plus biopsy in the presence of GVHD in another organ, while isolated hepatic GVHD was confirmed by biopsy. In the majority of patients, histopathological evidence was present for end-organ injury. In addition to hepatic dysfunction, serological studies were performed to assess active viral hepatitis. In patients with hepatitis B antigen positivity, the HBV-DNA was assessed using the polymerase chain reaction (PCR) technique. The HCV-RNA was not tested because there was no HCV antibody positivity. Drug hepatotoxicity was defined as impairment in liver functions tests within the first 2 weeks after transplantation without an established reason. Cyclosporine toxicity was defined as impaired liver function tests in patients with an elevated cyclosporine level accompanied by an elevated bilirubin level, the presence of suggestive clinical findings (including fluid retention, hypertension, renal failure), and exclusion of other reasons. The whole blood CMV-PCR analysis was performed to identify cytomegalovirus infection. The detection limit was within a range of 90–108 copies/mL. The values <42 copies/mL were considered negative, while the values <80 copies/mL were low positive, and >80 copies/mL were high positive. For iron accumulation, results of liver biopsy were taken into consideration, while for patients who did not undergo biopsy, the ferritin level was taken into consideration. The ferritin level range >400 ng/mL was considered to be an increased iron load in patients without any findings of infection.

The study was approved by the ethics committee of the Erciyes University (2014/471)

Table 1. Patients characteristics (n=300)

	n	%
Age, mean±SD	36.22±11.82	
Gender, male/female	198/102	
Underlying disease		
AML	144	48.0
ALL	73	24.3
Aplastic anemia	23	7.7
NHL	14	4.7
Others	46	15.3
Conditioning regimen		
BU-CY	145	48.3
CY-TBI	56	18.7
Me-T-Fu-ATG	21	7.0
Donor source, related		
HLA mismatch	287	95.7
Full-match	270	90.0
Haploidentical	30	10.0

SD: Standard deviation; ALL: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; NHL: Non-Hodgkin lymphoma; BU: Busulfan; CY: Cyclophosphamide; TBI: Total body irradiation; Me: Melphalan; T: Thiotepa; Fu: Fludarabine; ATG: Antithymocyteglobuline; HLA: Human leukocyte antigen

Statistical Analysis

Pearson's chi squared exact test was used to compare categorical variables. A p-value ≤0.05 was considered statistically significant. The Kaplan–Meier curves with the log-rank test were used to assess the survival. The survival was evaluated according to GVHD. Descriptive statistics are presented as the mean and standard deviation. Data were analyzed using the IBM SPSS version 22.

RESULTS

Table 1 presents patient characteristics and conditioning regimens. Among 300 patients included, 30 cases of allogeneic HSCT were performed from haploidentical donors and 13 cases from unrelated donors. Elevated liver function tests (transaminitis) were detected in 215 (71.7%) of the patients. The ALT/AST elevation was already present in 65 of these patients (30.2%) before HSCT (p<0.001; Table 2). No significant difference was detected between conditioning regimens regarding the development of abnormal liver function tests. When underlying causes were assessed in 215 patients with abnormal post-transplantation liver function tests, GVHD was found in 97 patients (43.6%); followed by drug-related hepatotoxicity in 55 patients (24.7%) and sepsis in 31 patients (13.9%). In addition, recurrence of underlying disease, SOS, active viral hepatitis, and steatohepatitis were other reasons for abnormal hepatic functions (Fig. 1). Biopsy results showing end-organ damage were present in 80% of the patients with GVHD. Diagnosis was made by clinical findings and laboratory results in the remaining patients. Table 3 presents a time frame for the AST/ALT elevation, which is among the most common causes of abnormal liver function tests. Of 215 patients with abnormal liver function tests, 41.8% died

Table 2. Certain factors and their effects on transaminitis and the survival status

	Liver function test					Survival status				Total		
	Abnormal		Normal		p	Alive		Exitus				p
	n	%	n	%		n	%	n	%	n	%	
Age, year					**0.01**							0.13
>50	24	11.2	19	22.4		20	11.6	23	18.1	43	14.3	
≤50	191	88.8	66	77.6	153	88.4	104	81.9	257	85.7		
Gender					0.89							0.17
Male	141	65.6	57	67.1		120	69.4	78	61.4	198	66	
Female	74	34.4	28	32.9		53	17.7	49	38.6	102	34	
Pretransplant transaminitis					**<0.001**							0.50
Yes	65	30.2	10	11.8		46	26.6	29	22.8	75	25	
No	149	69.8	75	88.2		127	73.4	98	77.2	225	75	
Underlying disease					**0.02**							0.60
Acute leukemia	167	77.7	50	58.8		123	71.1	94	74	217	72.3	
Others	48	22.3	35	41.2		50	28.9	33	26	83	27.7	
Iron overload					**<0.001**							**<0.001**
Yes	185	86	57	67.1		126	72.8	116	91.3	242	80.7	
No	30	14	28	32.9		47	27.2	11	8.7	58	19.3	
Relaps disease					0.27							**<0.001**
Yes	34	15.8	9	10.6		4	2.3	39	30.7	43	143	
No	181	84.2	76	89.4		169	97.7	88	69.3	257	85.7	
Pretransplant HBsAg positive					0.06							0.19
Yes	10	4.7	0	0		8	4.6	2	1.6	10	3.3	
No	205	95.3	85	100		165	95.4	125	98.4	290	96.7	
GVHD					**<0.001**							0.21
Yes	97	45.1	1	1.12		62	35.6	36	28.5	98	32.6	
No	118	54.9	84	98.8		112	64.4	90	71.5	202	67.4	
Total bilirubin												**<0.001**
2 mg/dl and above						9	5.2	28	22	37	12.3	
Below 2 mg/dl						164	94.8	99	78	263	87.7	

GVHD: Graft versus host disease

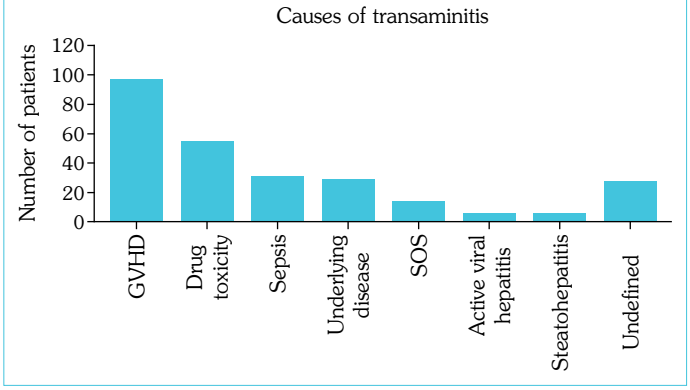

Figure 1. Causes of transaminitis in the post-transplantation period

GVHD: Graft-versus-host disease; SOS: Sinusoidal obstruction syndrome

(p=0.792), while this rate was 36.7% among patients who had abnormal liver function tests caused by GVHD (p=0.214), indicating no statistical significance. The survival time was not affected significantly by the presence of GVHD (Fig. 2). However, a significant correlation was found between the rate of death and hyperbilirubinemia (≥2 mg/dL) in patients with the ALT/AST elevation (p<0.001; Table 2). Moreover, it was also found that the mortality rate was significantly increased in patients experiencing recurrence during follow-up and those with increased iron load (p<0.001). The Kaplan–Meier curve of total survival according to relapse disease is given in Figure 3.

The mean survival time was 32.43±28.93 months with a median value of 23 months. Based on diagnosis, the longest mean survival was observed to be 40 months (range, 0–91 months) in patients with aplastic anemia. Considering all types of allogeneic transplantation (sibling, unrelated, haploidentical), 65.2% was calculated

Table 3. Timing in the three most common reasons of transaminitis

Timing, day	GVHD (n=97)		Drug toxicity (n=55)		Sepsis (n=31)	
	n	%	n	%	n	%
0–30	8	8.3	43	78.2	9	29
31–90	14	14.4	4	7.2	7	22.6
>91	75	77.3	8	14.6	15	48.4

GVHD: Graft versus host disease

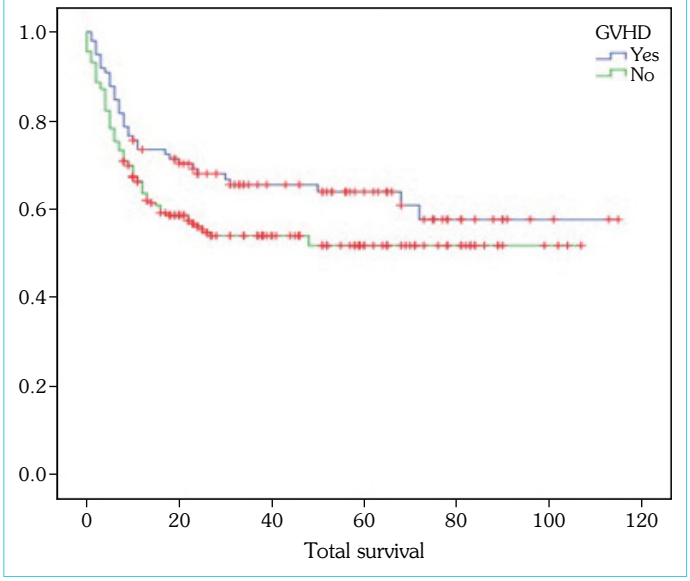

Figure 2. Survival graph according to GVHD
GVHD: Graft-versus-host disease

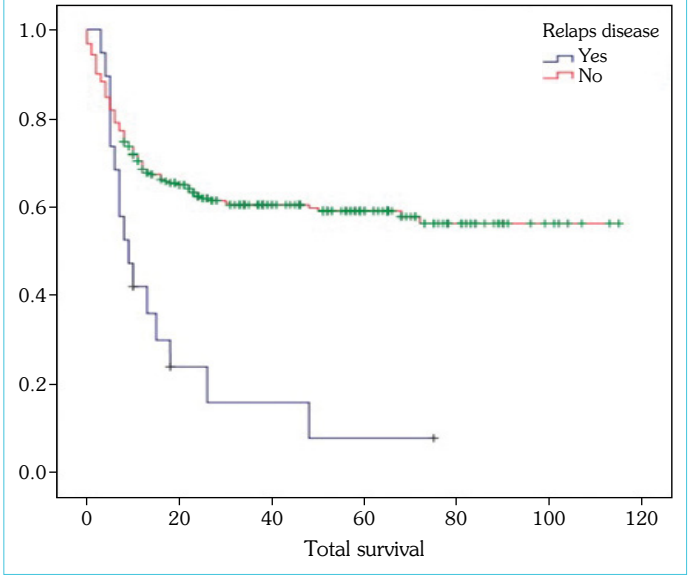

Figure 3. Survival graph according to relapse disease

for the 1-year overall survival, while 48.7% was calculated for the 2-year survival. Sepsis was the most common cause of death among 127 patients, who died after allogeneic HSCT, followed by the recurrence of main disease and GVHD. GVHD was observed in 98 (32.6%) patients along with elevated liver functions tests, which were present after transplantation in all patients but one.

In the baseline assessment, there was the HBsAg positivity in 10 patients, two of which had positive HBV DNA. No positive HCV antibodies were detected in patients. After transplantation, elevated liver function tests were detected in all patients with the HBsAg positivity (p=0.067), while hepatitis B activation was observed in 2 patients with the HBV DNA positivity.

DISCUSSION

Although the advances in alternative therapies have been developing rapidly (8, 9), allogeneic HSCT is still one of the most promising treatments in terms of achieving complete cure in patients with hematological malignancies. AML, ALL, and CML were the most common diagnoses in historical series of HSCT studies. In our study, acute leukemia comprised majority of the diagnosis in transplanted patients, and AML, ALL, and aplastic anemia were the three most common diseases (4, 6). CML is downgraded due to replacement of tyrosine kinase inhibitors instead of allogeneic HSCT in the treatment. In addition, in recent years, HSCT has been considered as an effective and successful therapeutic option in patients with aplastic anemia, and the HSCT rate has been increasing in these patients. Indeed, in this study, the lowest mortality rate and the highest mean survival were achieved in aplastic anemia, although the difference did not reach statistical significance.

In previous studies, the incidence of hepatic dysfunction was reported as 57.5%–82% in adult patients undergoing allogeneic HSCT (6, 4, 10). The highest rate of hepatic dysfunction was reported as 82% in a retrospective Korean study on 101 bone marrow transplantation recipients (6). In studies from the pediatric age group, this rate was slightly lower. In a study that included both children (26%) and adults, Jordan et al. showed transaminitis in 52% of patients, and they suggested that even mild liver affection following HSCT is predictive of a poor long-term survival (11). In our study, the rate of hepatic dysfunction was markedly high (71.7%). It was seen that the majority of patients who had transaminitis before transplantation developed hepatic dysfunction after transplantation as well (p<0.001). After transplantation, transaminitis developed in 10 of 10 patients who were initially HBsAg positive (p=0.067), indicating the importance of a pre-transplantation assessment. Previous studies showed that elevated liver enzymes due to any reason and the HBsAg positivity before transplantation are independent risk factors (10). Our findings support previous studies. It is important to be careful and pay attention to patients with viral hepatitis before transplantation, particularly in those countries with a higher incidence of HBV and HVC infections, such as Turkey (8%–10% and 1%–3%, respectively) (12, 13). There are studies and guidelines indicating that prophylactic and preemptive therapies are useful in eligible cases (14, 15). In our clinic, antiviral prophylaxis was provided for hepatitis B carriers or those with immunity during the HSCT process. Given that the post-transplantation hepatic injury increases mortality while decreasing survival, a careful pre-transplantation assessment and prophylaxis will improve the success of transplantation.

In the literature, the most common causes of hepatic dysfunction have been reported as GVHD (33%–40.6%), drug toxicity (19%–30%), and viral hepatitis (7%–15%) in allogeneic transplantations (4). In our study, the most common cause was GVHD in patients with post-transplantation hepatic dysfunction. When considering the time frame, drug toxicity was the most common cause within the 1st month after transplantation, while GVHD was more common after 1 month. Other causes included sepsis, recurrence, SOS, and viral hepatitis. The sepsis rate was 14.4%, as being rather common among other causes. It was found that one-third of cases developed within 1st month and that sepsis was the most common cause of mortality. This emphasizes the importance of shortening the period as much as possible, the management of sepsis for prolonging survey, and protecting liver functions.

In a multicenter study conducted in 2015, it was found that chronic GVHD incidence was increased over time, but there was no change in risk factors in patients undergoing allogeneic HSCT. Authors emphasized the improvement in supportive therapies and prolonged survival in this result (16). It is known that both acute and chronic GVHD are associated with a decreased survival (16–18). Although survival was better in the presence of GVHD, no significant association was found between a better survival and GVHD. No decrease in survival, at least, can be explained by success of regimens used in the GVHD prophylaxis, early diagnosis of GVHD, and appropriate therapeutic approaches to GVHD.

SOS is a cause of hepatotoxicity, which is often associated with preparation regimens, and it was found in 14 patients (6.5%) in our study. It is more frequently observed in transplantation procedures using cyclophosphamide or busulfan. In previous studies, SOS was reported as a cause of abnormal liver function tests in a wide spectrum, ranging from 1% to 64% (19, 20). Similar to our study, busulfan plus cyclophosphamide and cyclophosphamide plus TBI were the most common preparation regimens in these studies. In previous studies, a wide variation in the SOS incidence might be due to the intensity of regimens used. In addition, the presence of risk factors (transplant type, unrelated donor, HLA incompatibility, stem cell harvested from the bone marrow, advanced age, comorbid liver disease, history of radiation exposure and previous SOS, pretransplantation transaminitis, etc.) other than drug toxicity leads to a heterogeneous patient profile. Given its higher mortality, it is important to prevent the SOS development. For this purpose, it can be more reasonable to identify individual risk groups, avoids high-risk regimens for SOS, and to use nonmyeloablative regimens without hepatotoxicity. Like in our clinic, some facilities apply ursodeoxycholic acid (UDCA)-based prophylactic approaches to prevent SOS or to decrease severity of SOS.

Hepatic injury-related mortality rate has been reported from 4% to 15% in different series with the mortality rate up to 80% (3). Thus, abnormal liver function tests are an important, concerning problem in transplant patients. Previous studies showed a strong association between the total bilirubin level and mortality (11). In our study, no significant direct correlation was found between the AST/ALT elevation and mortality, while mortality was significantly increased in the presence of hyperbilirubinemia (>2 mg/dL) together with the AST/ALT elevation. This result from such a finding indicates a more severe clinical picture due to the involvement of the biliary tract, in addition to the parenchymal injury. Similarly, it was seen that the pretransplantation ALT/AST elevation alone had no effect on survival. However, it was more likely to develop transaminitis following transplantation in patients who already had the ALT/AST elevation before transplantation. There are three major studies on the effects of pretransplantation ALT/AST levels on post-transplantation outcomes. In two of these studies, it was concluded that pretransplantation transaminase levels affect the outcomes of transplantation (21, 22). Parallel to our study, Barba et al. suggested that pretransplantation transaminase levels are not useful mortality and survival predictors, advocating that the pretransplantation bilirubin level is a better predictor for mortality (23). In a more recent study that included 81 patients, the association between survival and a lower bilirubin level, rather than the transaminase level, was emphasized (20). In our view, it will be helpful to monitor bilirubin levels together with ALT/AST levels.

In patients with HSCT, anemia is frequently encountered due to both effects of chemotherapeutic treatments and the bone marrow suppression effect of the primary disorder. Transfusions used in the management of anemia lead to undesired iron accumulation with an increased burden of iron, resulting in several complications, such as abnormal liver function tests and SOS (24). In addition, iron accumulation predisposes to infections by disrupting cellular and humoral immunity. In studies categorizing patients with HSCT, according to the serum ferritin level, an overall survival rate was found to be lower in patients with higher ferritin levels, while complications such as infection, recurrence, and GVHD were higher in these patients (25–27). Similarly, it was observed that the hepatic dysfunction and mortality rates were higher in patients with iron accumulation as shown by biopsy and laboratory evaluations in our study. Thus, it is of major importance to assess the iron status before transplantation. The serum ferritin level measurement is the most widely used method for the assessment of iron status. Iron chelation therapy before, if possible, and after transplantation may have positive effects on outcomes. There is no prospective, randomized study on the effects of chelation therapy. Further comprehensive studies on this issue may help to improve the success of HSCT, a promising option in the treatment of malignancies.

In the literature, there are studies suggesting that the post-transplantation recurrence is the most significant parameter of mortality (16, 28). Although it is not the primary aim our study, it was found that the recurrence caused a significant increase in mortality, which is in agreement with previous studies.

CONCLUSION

In conclusion, hepatic dysfunctions are a common condition occurring after transplantation, and transaminase levels are used to monitor hepatic dysfunction in almost all clinics. In our study, the recurrence after transplantation is due to iron accumulation and bilirubin level >2 mg/dL in association with hepatic dysfunction at the post-transplantation period, which appeared to be major factors influencing mortality following transplantation. It was observed that the AST/ALT elevation significantly increased mortality only in the case of hyperbilirubinemia and iron accumulation. For a successful management of transplantation, it is important to monitor liver functions before and after transplantation, and to identify risk factors.

Ethics Committee Approval: The study was approved by the ethics committee of the Erciyes University (date: 01.08.2014, number: 2014/471).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MK, LK; Design – MK, LK; Supervision – EY, LK; Resource – MK; Materials – MK, AU, MC, BE, LK; Data Collection and/or Processing – MK; Analysis and/or Interpretation – MK, EY; Literature Search – MK, EY; Writing – MK, EY; Critical Reviews – AU, BE, MC, EY, LK.

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