Impact of Hypothyroidism on Patients with Hepatocellular Carcinoma Undergoing Liver Transplantation

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Background: This work endeavored to explore the effect of hypothyroidism on mortality in subjects with HCC who underwent living-donor liver transplantation (LDLT).

Methods: This prospective study included 107 patients with HCC subjected to LDLT, divided into hypothyroid group (n=53) and euthyroid group (n=54). The primary objectives were overall and disease-free survival (DFS).

Results: Euthyroid and hypothyroid groups were comparable in all baseline characteristics except the age of patients. Overall survival (OS) of the whole group at 48 months was 68.8%, while the DFS was 60.2%. On univariate analysis, OS was negatively affected by the older age of the patients (p<0.001) or the donor (p=0.005), hypothyroidism (p=0.008), HBV (p=0.029), larger tumor size (p=0.023), and defective Milan criteria (p=0.022). On multivariate analysis, the age of the patients and donors was the independent factor affecting OS. On univariate analysis, DFS was negatively affected by older age of the patients (p < 0.001) or the donor (p=0.005), hypothyroidism (p=0.005), HBV (p=0.019), larger tumor size (p=0.023), and defective Milan criteria (p=0.020). On multivariate analysis, the age of the patients, thyroid status, and Milan criteria were the independent factors affecting DFS.

Conclusion: Hypothyroidism is a risk factor for worse outcomes in HCC patients after liver transplantation.

Keywords: hypothyroidism, hepatocellular carcinoma, liver transplantation

Introduction

Globally, hepatocellular carcinoma (HCC) is the most frequent primary liver cancer representing the sixth most common malignancy.1 In Egypt, HCC is the fourth common cancer.2 The age-standardized incidence rate of HCC is 61.8 per 100,000 population.3 The pathogenesis of HCC is a complex process linked to different predisposing factors. Liver cirrhosis is a chief risk factor for HCC development irrespective of its cause. Meanwhile, chronic viral infections, hepatitis B virus (HBV), and hepatitis C virus (HCV) are substantial risk factors for HCC.4 Metabolic5 and hormonal factors6 were suggested to be implicated in the development of HCC.

Growing evidence indicated the involvement of thyroid hormones in the development of malignancies of the breast,7 ovary,8 and HCC.9 Thyroid hormones (TH) are involved in regulating several physiological processes, such as cell development, structure, growth, and metabolism.10 Thyroid disorders are commonly linked to many chronic comorbidities like diabetes mellitus,11 chronic kidney disease,12

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and liver disorders. Epidemiological data supposed a positive correlation between hypothyroidism and high risk of NAFLD and HCC. Besides, experimental studies found that treatment with T3 can prevent liver diseases, including HCC in rodents exposed to carcinogens.

These findings back a possible role TH in the progression and survival in patients with HCC. Therefore, the current work endeavored to explore the effect of hypothyroidism on mortality in patients with HCC undergoing liver transplantation.

**Patients and Methods**

This prospective multicentre cohort analysis involved 107 cases aged 18 years or more with HCC who underwent living-donor liver transplantation. The patients were divided into two groups according to the thyroid status: hypothyroid group (n=53) and euthyroid group (n=54). Patients were excluded if diagnosed with cholangiocarcinoma (CCA), mixed HCC, and CCA or fibrolamellar HCC based on explant pathology. Also, patients who developed hypothyroidism due to treatment of hyperthyroidism were not enrolled in the analysis.

The work was approved by the relevant ethical committee of Cairo and Al-Azhar University Hospitals and the National Liver Institute. All living-donor transplants were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul. Also, this study was conducted in accordance with the Declaration of Helsinki.

The confirmation of HCC was based on either noninvasive parameters (a new lesion >1 cm in size evolving in a cirrhotic patient and depicted by arterial hyperenhancement and portal venous washout on computed tomography, magnetic resonance imaging, or angiography) or histopathology from the biopsy or the explanted liver, adopting the criteria of the American Association for the Study of Liver Disease (AASLD) 2010 Guidelines for HCC. All cases were followed up for a median of 43 months (range: 1–58).

**Data Collection**

Demographic data, medical background, smoking history, laboratory workup, original liver disorders (including symptoms that indicate decompensation such as repeated spontaneous bacterial peritonitis (SBP), repeated hepatic coma, refractory fluid retention, and recurrent variceal bleeding), and HCC features from the explanted liver were registered. Medical history before the diagnosis of HCC, such as uncontrolled blood sugar, elevated blood pressure, hyperlipidemia, and hypothyroidism, were collected.

Pretransplant hypothyroidism was determined as a thyroid-stimulating hormone (TSH) level continuously over the year preceding transplant >5 mIU/L, a previously confirmed endocrinologist diagnosis, or the usage of thyroid hormone replacement medications.

Original hepatic diseases were confirmed by positive HBsAg for HBV, positive HCV RNA or anti-HCV for HCV, previous undue alcohol consumption for alcoholic liver disease (ALD), metabolic syndrome associated with fatty infiltration for non-alcoholic fatty liver disease (NAFLD), and immunological and/or histopathologic confirmation for autoimmune liver diseases (AILD) including autoimmune hepatitis, primary biliary cholangitis, primary sclerosis cholangitis, and others. Cases were followed up for five years from the time of liver transplantation or till death.

The primary outcomes were overall and disease-free survival and recurrence rate. Overall survival was calculated from the time of operation to the time of death or last follow-up visit. Disease-free survival was calculated from the time of operation to the time of recurrence, death, or last follow-up.

**Anesthetic Management**

During the transplantation procedure, all patients were anesthetized by IV propofol (2mg/kg), Fentanyl (2mic/kg), and rocuronium (0.9 mg/kg) as a neuromuscular blocker, and blouses were given according to neuromuscular monitor and maintained by inhaled sevoflurane.

Lungs will be controlled by pressure-regulated volume-controlled mode, with a mixture of (Fio2 0.4) in air, and PEEP was applied after recruitment, PaCo2 was adjusted around 35 mmHg.

Rotational thromboelastometry (ROTEM) was used to guide transfusion of platelets, fresh frozen plasma, and cryoprecipitate perioperatively.

**Sample Size**

In a recent work, the median survival time of euthyroid cases was nearly 12 years, the accrual interval was one year, and additional follow-up after the accrual interval of 15 years. If the true hazard ratio (relative risk) of hypothyroid cases relative to euthyroid cases is 2.45, 48 hypothyroid patients and 48 euthyroid (total 96) patients
were needed to be able to reject the null hypothesis that the hypothyroid and euthyroid survival curves are equal with a power of 0.80. An additional 10% was added to compensate for expected losses; the total sample is 107 patients (53 per group). The Type-I error probability associated with this test of this null hypothesis is 0.05. The sample size was estimated using power and sample program version 3.1.2.

Results
Follow-up started immediately post-transplantation. Cases were followed up for five years from the time of liver transplantation or till death.

The euthyroid and hypothyroid groups were comparable in all of the baseline characteristics except for the age of the patients (Table 1). The hypothyroid group was significantly older than the euthyroid group (p = 0.007). There were no considerable differences between the two groups in terms of all of the tumor characteristics and laboratory tests (Tables 2 and 3). TSH levels were significantly higher in the hypothyroid group, as this was the basis of group categorization.

The overall survival of the whole group at 48 months was 68.8%, while the DFS was 60.2% (Table 4). On univariate analysis overall survival was negatively affected by older age of the patients (p < 0.001) or the donor (p < 0.001), hypothyroidism (p = 0.008), HBV (p = 0.029), larger tumor size (p = 0.023), defective Milan criteria (p = 0.022), and recurrent gastrointestinal bleeding (p = 0.036). On multivariate analysis, the age of the patients and donors were the independent factors affecting overall survival (Table 5).
Table 2 Tumor Characteristics of the Two Studied Groups

|                          | Euthyroid Group n=54 | Hypothyroid Group n=53 | p-value |
|--------------------------|-----------------------|------------------------|---------|
| Differentiation          |                       |                        |         |
| No viable tumor          | 11 (20.4%)            | 12 (22.6%)             | 0.793   |
| Well and moderate        | 31 (57.4%)            | 27 (50.9%)             |         |
| Poorly and undifferentiated | 12 (22.2%)           | 14 (26.4%)             |         |
| Tumor number             |                       |                        |         |
| Solitary                 | 29 (53.7%)            | 24 (45.3%)             | 0.311   |
| Two                      | 14 (25.9%)            | 21 (39.6%)             |         |
| More than two            | 11 (20.4%)            | 8 (15.1%)              |         |
| Tumor diameter           |                       |                        |         |
| <3 cm                    | 25 (46.3%)            | 24 (50.9%)             | 0.463   |
| 3-5 cm                   | 21 (38.9%)            | 15 (28.3%)             |         |
| >5 cm                    | 8 (14.8%)             | 11 (20.8%)             |         |
| Within Milan criteria    | 48 (88.9%)            | 46 (86.8%)             | 0.740   |
| Vascular invasion        | 4 (7.4%)              | 6 (11.3%)              | 0.487   |
| Recurrent Spontaneous peritonitis | 11 (20.4%) | 13 (24.5%) | 0.606 |
| Recurrent GI Bleeding    | 11 (20.4%)            | 12 (22.6%)             | 0.775   |
| Recurrent encephalopathy | 9 (16.7%)             | 8 (15.1%)              | 0.824   |
| Resistant Ascites        | 6 (11.1%)             | 5 (9.4%)               | 0.775   |
| Bridge treatment         | 19 (35.2%)            | 20 (37.7%)             | 0.784   |

Note: Data are summarized as Number (%).
Abbreviation: GI, gastrointestinal.

Table 3 Results of Laboratory Tests of the Two Studied Groups

|                          | Euthyroid Group n=54 | Hypothyroid Group n=53 | p-value |
|--------------------------|-----------------------|------------------------|---------|
| TSH (mIU/L)              | 2.4±0.7               | 4.2±1.3                | <0.001  |
| Hemoglobin (gm/dL)       | 9.7±1.1               | 9.6±1.2                | 0.790   |
| Total leukocytic count (x10^3/mm^3) | 7.3±1.9             | 7.9±2.0                | 0.132   |
| Platelets count (x10^3/mm^3) | 187.0 (59.0–422.0) | 176.0 (46.0–387.0) | 0.803   |
| Serum Albumin (mg/dL)    | 3.1±0.6               | 3.2±0.6                | 0.567   |
| Total bilirubin (mg/dL)  | 2.0±0.4               | 2.0±0.5                | 0.436   |
| AST (IU/L)               | 62.0 (34.0–87.0)      | 55.0 (32.0–110.0)      | 0.104   |
| ALT (IU/L)               | 45.5 (25.0–78.0)      | 43.0 (24.0–84.0)       | 0.201   |
| INR                      | 1.7±0.3               | 1.8±0.3                | 0.457   |
| Alpha fetoprotein (IU)   | 74.0 (12.0–453.0)     | 68.0 (10.0–365.0)      | 0.866   |
| Glomerular filtration rate | 87.1±11.4            | 86.8±10.5             | 0.870   |
| MELD score               | 14.2±2.2              | 14.2±2.3               | 0.900   |

Note: Data are presented as mean±SD.
Abbreviations: TSH, Thyroid-stimulating Hormone; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; INR, The international normalized ratio; MELD, Model for End-stage Liver Disease.
Table 4 Cumulative Overall and Disease-Free Survival Proportion of the Two Studied Groups in Relation to the Possible Patient and Tumor Factors

|                       | n     | Cumulative OS at 48 Months (%) | p-value      | Cumulative DFS at 48 Months (%) | p-value  |
|-----------------------|-------|--------------------------------|--------------|----------------------------------|----------|
| Whole Group           | 107   | 68.8                           |              | 60.2                             |          |
| Age (years)           |       |                                |              |                                  |          |
| ≤ 50                  | 77    | 81.7                           |              | 69.7                             | <0.001   |
| > 50                  | 30    | 36.5                           | <0.001       | 37.1                             | <0.001   |
| Thyroid Status        |       |                                |              |                                  |          |
| Euthyroid             | 54    | 79.9                           | 0.008        | 71.9                             | 0.005    |
| Hypothyroid           | 53    | 57.5                           |              | 47.8                             |          |
| Donor Age (years)     |       |                                |              |                                  |          |
| ≤ 30                  | 55    | 90.9                           | <0.001       | 71.8                             | 0.005    |
| > 30                  | 52    | 46.2                           |              | 48.0                             |          |
| Diabetes Mellitus     |       |                                |              |                                  |          |
| No                    | 73    | 71.8                           | 0.938        | 64.4                             | 0.564    |
| Yes                   | 34    | 68.5                           |              | 66.1                             |          |
| Hypertension          |       |                                |              |                                  |          |
| No                    | 93    | 74.1                           |              | 67.3                             |          |
| Yes                   | 14    | 47.1                           | 0.116        | 48.2                             | 0.186    |
| Dyslipidemia          |       |                                |              |                                  |          |
| No                    | 83    | 71.8                           | 0.410        | 65.6                             | 0.286    |
| Yes                   | 24    | 66.7                           |              | 53.6                             |          |
| HCV                   |       |                                |              |                                  |          |
| No                    | 60    | 70.9                           | 0.880        | 65.6                             | 0.620    |
| Yes                   | 47    | 65.8                           |              | 51.1                             |          |
| HBV                   |       |                                |              |                                  |          |
| No                    | 89    | 75.3                           | 0.029        | 67.5                             | 0.019    |
| Yes                   | 18    | 46.3                           |              | 39.5                             |          |
| Differentiation       |       |                                |              |                                  |          |
| No viable tumor       | 23    | 68.6                           |              | 59.6                             |          |
| Well and moderate     | 26    | 58.9                           |              | 43.8                             |          |
| Poorly and undifferentiated | 58 | 72.6                           | 0.298        | 69.0                             | 0.098    |
| Tumor Number          |       |                                |              |                                  |          |
| Single                | 53    | 64.7                           |              | 59.0                             | 0.509    |
| Multiple              | 54    | 72.6                           | 0.626        | 59.3                             |          |
| Tumor Size            |       |                                |              |                                  |          |
| ≤ 3 cm                | 52    | 56.9                           | 0.023        | 54.9                             | 0.232    |
| > 3 cm                | 55    | 80.3                           |              | 62.5                             |          |
| Within Milan          |       |                                |              |                                  |          |
| No                    | 13    | 46.2                           |              | 36.9                             | 0.020    |
| Yes                   | 94    | 74.2                           | 0.022        | 63.6                             |          |
| Vascular invasion     |       |                                |              |                                  |          |
| No                    | 97    | 73.1                           | 0.150        | 65.3                             | 0.139    |
| Yes                   | 10    | 60.0                           |              | 40.0                             |          |
| Bridge treatment      |       |                                |              |                                  |          |
| No                    | 68    | 66.5                           | 0.679        | 61.7                             | 0.650    |
| Yes                   | 39    | 60.5                           |              | 56.5                             |          |
| Recurrent Spontaneous peritonitis |     |                                |              |                                  |          |
| No                    | 83    | 74.0                           | 0.248        | 63.8                             | 0.314    |
| Yes                   | 24    | 60.0                           |              | 50.6                             |          |
| Recurrent GIT Bleeding|       |                                |              |                                  |          |
| No                    | 84    | 74.7                           | 0.036        | 64.3                             | 0.087    |
| Yes                   | 23    | 48.5                           |              | 46.4                             |          |

(Continued)
Table 4 (Continued).

| Disease-Free Survival | n       | Cumulative OS at 48 Months (%) | p-value | Cumulative DFS at 48 Months (%) | p-value |
|-----------------------|---------|-------------------------------|---------|-------------------------------|---------|
| Recurrent Encephalopathy | No 90   | 72.8                          | 0.096   | 61.7                          | 0.222   |
|                       | Yes 17  | 58.8                          |         | 52.9                          |         |
| Resistant Ascites     | No 96   | 74.1                          | 0.094   | 62.1                          | 0.184   |
|                       | Yes 11  | 45.5                          |         | 45.5                          |         |

**Abbreviations:** HCV, hepatitis C virus; HBV, hepatitis B virus.

On univariate analysis disease-free survival was negatively affected by older age of the patients (p < 0.001) or the donor (p = 0.005), hypothyroidism (p = 0.005), HBV (p = 0.019), larger tumor size (p = 0.023), and defective Milan criteria (p = 0.020).

On multivariate analysis, age of the patients, thyroid status and Milan criteria were the independent factors affecting DFS (Table 5).

**Discussion**

This study demonstrated that in patients with HCC undergoing liver transplantation, hypothyroidism is an independent factor that negatively affected disease-free but not overall survival. In these cases, the older age of the patients and liver donors were the independent factors worsening overall survival. Older age of the patients, hypothyroidism and Milan criteria were the independent factors affecting disease-free survival.

A great deal of research indicated a potential role of thyroid hormones in the pathogenesis of various cancer types. A previous study suggested that hyperthyroidism increases the hazard of some solid tumors, while hypothyroidism may decrease aggressiveness or delay the onset of malignancy.

This may be logical as thyroid hormones can exert a tumor-promoting effect. However, an opposite conclusion provoked by a recent systematic review of 14 studies concluded that hypothyroidism was linked to an increased risk of HCC and colorectal cancer and conversely decreased risk of prostate cancer.

In a case-control study, Reddy et al suggested that hypothyroidism is an independent risk factor for developing HCC. This was based on a significantly higher likelihood of hypothyroidism in cases with HCC of unknown etiology than those with known etiology. A larger case-control study, including 420 HCC patients, found that a history of hypothyroidism in women for more than ten years increased the risk of developing HCC. In contrast, this association was not observed in men.

These findings enthused research on the molecular mechanisms through which hypothyroid status may promote tumorigenesis. Circulating thyroid hormones (THs) interact with thyroid hormone receptors (THRs) encoded by the TRα and TRβ genes. THs exert their effect via two mechanisms: stimulation of target gene expression through TRα and TRβ and a rapid, transcription-independent (nongenomic) effect. These receptors are ligand-dependent transcription factors belonging to the nuclear receptors superfamily. These receptors are reported to affect cell proliferation and malignant transformation. The liver is an important

**Table 5 Multivariate Cox Regression Analysis for Independent Factors Affecting Overall and Disease-Free Survival on the Whole Studied Group (n=107)**

|                      | Regression Coefficient (B) | Hazard Ratio | 95% Confidence Interval of Hazard Ratio |
|----------------------|----------------------------|--------------|----------------------------------------|
| **Overall Survival** |                           |              |                                        |
| Recipient age        | 1.119                      | 3.063        | 1.462–6.418                            |
| Donor age            | 1.611                      | 5.009        | 1.874–13.389                           |
| **Disease-free Survival** |                       |              |                                        |
| Thyroid status       | 0.730                      | 2.074        | 1.062–4.050                            |
| Recipient age        | 0.977                      | 2.655        | 1.374–5.130                            |
| Within Milan criteria| 0.925                      | 2.521        | 1.137–5.593                            |

**Note:** All variables mean that the higher values contribute to higher risk.
target organ of TH; hence, disruption of cellular TH-THRs signals is recognized to initiate liver diseases as chronic hepatitis and HCC.\textsuperscript{17,26} For example, reduced expression of TRs is a common event in many human cancer.\textsuperscript{16,27–29} Inactivating mutations in TRs that block access to the target genes has been detected in +70% of HCC patients.\textsuperscript{30,31} Also, v-Erba, a mutant form of THRA missing the ability of ligand binding, is reported to cause HCC in transgenic mice.\textsuperscript{32} In addition to maintaining hepatic homeostasis, the TH-THRs pathway acts as a tumor repressor in the liver.\textsuperscript{17}

In the present work, hypothyroidism was an independent factor that impacted disease-free survival in those with HCC after liver transplantation. A plausible explanation for these findings was the data reported by Chi et al, who have shown that disruption of TH production induced marked progression of diethylnitrosamine (DEN)-induced HCC in a murine model. The administration of TH resulted in suppressing the carcinogenic process through the activation of autophagy.\textsuperscript{17} Other studies in animal models indicated the critical role of normal autophagic flux in preventing HCC development.\textsuperscript{33,34} Autophagy is a bulk degradation system of the impaired components of aggregated proteins in lysosomes to maintain cellular homeostasis.\textsuperscript{35} In a rat model, the down-regulation of TRs, especially Trβ was an early event of the process of HCC carcinogenesis that heralds neoplastic transformation.\textsuperscript{36}

In the current study, we took a step forward to investigate the impact of hypothyroidism on the outcome of HCC patients following liver transplantation. We found a negative effect of hypothyroidism on the survival of HCC patients, but why it was associated with worse outcomes is not clear. Findings of the previous studies focusing on the development of HCC might provide a reasonable explanation of the results of the current study. These studies indicated that hypothyroid status, whenever untreated, could promote HCC progression and consequently worsen overall and disease-free survival.

This study is not without limitations. The restricted sample size of a single-center study should be considered. Besides, the study did not investigate the mechanism by which hypothyroid status may exert its action.

**Novelty of the Study**

It is sensible to say that there is very scarce research that addressed the impact of hypothyroidism on patients with HCC after liver transplant. We have found only a single article indicating a poorer overall and recurrence-free survival in HCC patients having liver transplantation in the association of hypothyroidism.\textsuperscript{21} Nonetheless, this study was a retrospective one, including 288 patients. Notably, among the strengths of this work are the prospective nature and the reasonable number of cases with a pretty extended follow-up period.

Furthermore, the study provided epidemiological evidence that can be a nucleus for further research on the molecular basis of unsatisfactory outcomes associated with hypothyroidism.

We can conclude that hypothyroidism represents a risk factor for worse outcomes in HCC patients after liver transplantation. It was linked to poorer overall survival, and it independently worsens disease-free survival in these patients. More extensive multi-center studies are needed to confirm these findings, which may add a significant addition to the treatment of HCC patients after liver transplantation.

**Disclosure**

The authors declare that there is no conflicts of interest in this work.

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