New-onset diabetes mellitus after liver transplantation in the patients with acute liver failure: is there any effect of pretransplant hypoglycemia?

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Abstract

Background: The frequency of new-onset diabetes after transplant (NODAT) is 5-30% in liver transplant recipients.

Aims: We aimed to analyze the frequency and predictors of NODAT in the patients undergoing liver transplantation (LTx) due to acute liver failure (ALF), and to investigate whether pretransplant hypoglycemia had any effect on NODAT.

Methods: Adult patients undergoing LTx due to ALF were analyzed retrospectively. The patients with chronic liver failure or diabetes were excluded. We measured pretransplant random blood glucose (RBG) and posttransplant fasting blood glucose (FBG). NODAT was diagnosed according to principally 1st month FBG (group 1: <100, group 2: 100-125, group 3: >125 mg/dL). The participants were subgrouped according to age, gender, BMI, etiology, antiviral medication, thyroid function, pretransplant RBG, donor type, immunosuppressive drug, common infection, and surgical complication.

Results: A total of 91 patients were analyzed; mean age was 33.48(±13.35), and 52.7% (n=48) of them was female. The etiology was Budd-Chiari syndrome in 3(3.29%), acute viral hepatitis in 38(41.75%), drug or toxin-related in 21(23.07%), and other/unknown causes in 29(31.86%) patients. The ratio of NODAT was 26.98% on the 1st month. NODAT group had a higher pretransplant RBG than the others. Pretransplant hypoglycemia did not have any effect on NODAT; however, pretransplant hyperglycemia increased the risk of NODAT by 4.065 times (p=0.018).

Conclusions: We showed that pretransplant hyperglycemia increased the risk of NODAT by 4 times, but hypoglycemia did not affect. The frequency of NODAT decreased progressively during follow-up. We recommend perioperative glycemic control should be maintained as early as possible to manage NODAT; however, it might be complicated in such a clinical condition.
Introduction

New-onset diabetes after transplant (NODAT) may develop in the patients after transplantation of solid organs such as liver, kidney, lung or heart [1-3]. It may be diagnosed with the same criteria as the nontransplant population at any time after transplantation [4]. However, oral glucose tolerance test may be sensitive but not a practical method for transplant patients; and HbA1c may be used for the diagnosis after 3rd month of transplantation [1,5].

The prevalence of NODAT was found as 5-30% in liver transplant recipients [6,7]. Preexisting prediabetes, obesity, hypertension, dyslipidemia or HCV infection, and posttransplant use of immunosuppressive drugs, posttransplant weight gain, CMV infection or acute rejection may increase the risk of occurrence of diabetes after liver transplantation (LTx) [2,8]. NODAT was shown to be associated with higher rate of rejection, cardiovascular morbidity, fatal infections, neurological complications, poor graft survival, and mortality in liver transplant recipients [9,10]. LTx may be indicated in the patients with acute liver failure, cirrhosis, hepatic neoplasm, or metabolic liver disease [6]. Several etiological factors may cause acute liver failure, such as acute viral hepatitis, drug or toxin induced acute liver failure, Budd-Chiari syndrome, ischemic hepatitis, hepatectomy or acute fatty liver of pregnancy.

In some studies, diabetes mellitus (DM) had been proposed to be an independent risk factor for ALF [11,12]. It was also reported that preexisting DM had no effect on the prognosis of ALF [13]. Besides, in acute liver failure (ALF), hypoglycemia may be observed due to a defect in glycogenolysis and gluconeogenesis, and the frequency of hypoglycemia was shown as about 45% in this patient population [14-16]. Hence, even in the absence of the coexistent DM, pretransplant glycemic status may be different in the patients with ALF.
than those with chronic liver failure. However, the frequency of NODAT has not been studied as a comparison between acute and chronic causes of liver failure yet [6,7]. Moreover, it is not known whether there is any effect of the development of hypoglycemia on the emergence of NODAT in the patients undergoing LTx due to ALF. There is no report analyzing the risk factors of NODAT in this patient population. We aimed to analyze the frequency and possible predictors of NODAT in the patients undergoing LTx due to ALF, and to investigate whether pretransplant hypoglycemia had any effect on the development of NODAT.

Materials And Methods

Adult patients who admitted to our clinics with a diagnosis of ALF and underwent LTx between 2010 and 2018 were included in our study. ALF may be defined as coexistence of severe acute liver injury, hepatic encephalopathy and dysfunction of hepatic synthesis of proteins and coagulation factors (international normalized ratio ≥1.5) in the patients without preexisting liver disease [17]. We diagnosed the patients as ALF based on the clinical and laboratory features, and accepted duration cutoff to discriminate ALF from chronic liver disease as 26 weeks. We considered several clinical conditions as a cause of ALF, such as Budd-Chiari syndrome (BCS), acute viral hepatitis, drugs and toxins, and the other/unknown etiological factors in our study. The patients younger than 18-year-old, those with chronic liver failure, known type 1 or 2 DM, taking any antidiabetic regimen, or lacking data were not included in our study.

Our study was designed as retrospective manner and approved by the Ethics Committee of our university, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective design of the study and the use of already available data, written informed
consent was unavailable.

Basic demographic (age) and clinical (height, weight, body mass index) features were recorded preoperatively and analyzed. Body weight (kg) and height (m) were measured with patient barefoot and having light clothes. Body mass index (BMI) was calculated as weight/square of height (kg/m²).

Baseline laboratory findings were measured and analyzed. We measured random venous blood glucose (RBG) before LTx on admission, and fasting blood glucose (FBG) on the 1st and 7th day, on the 1st, 3rd, and 12th month of LTx after an overnight fasting for at least 8 hours. We evaluated the patients according to FBG levels, and diagnosed as NODAT based on the diagnostic criteria of DM [4]. We analyzed the patients principally according to the 1st month FBG. We could not measure FBG before LTx due to unstable clinical condition of the patients. Blood glucose was designated as mg/dL, TSH mIU/L, free T4 (fT4) ng/dL, free T3 (fT3) pg/mL. Blood glucose was measured from venous blood sample by glucose oxidase method with the Olympus AU-2700 analyzer. TSH, fT4, and fT3 were measured with chemiluminescence method by using the Beckman Coulter marked and Dxi 800 model device (Beckman Coulter, Inc. 4300 N. Harbor Blvd., Fullerton, CA 92835 U.S.A.). The reference range of our laboratory was used to determine the upper and lower limit of normal for all laboratory parameters.

The participants were subgrouped according to age (<40 vs ≥40), gender (female vs male), BMI (<30 vs ≥30 kg/m²), etiology (other vs acute viral hepatitis), antiviral medication (absence vs presence), thyroid function (euthyroid vs subclinical
thyrotoxicosis), pretransplant RBG (hypoglycemia: <54/≥54 or <70/≥70 mg/dL, or hyperglycemia: <200/≥200 mg/dL), donor type (cadavr vs living donor), immunosuppressive drug (tacrolimus vs other), common infection (absence vs presence), surgical complication (absence vs presence), and posttransplant FBG (group 1:<100 mg/dL, group 2:100-125 mg/dL, group 3:>125 mg/dL). Subclinical thyrotoxicosis was defined as TSH lower than normal limits, with fT4 and fT3 level in the reference range. We defined pretransplant hypoglycemia according to alert value (70 mg/dL) or clinically important hypoglycemia threshold (54 mg/dL) based on the report of International Hypoglycemia Study Group [18]. We defined common infection as upper respiratory or urinary tract infection, and surgical complication as common biliary or vascular complications which might be observed in the postoperative period.

**Statistical analysis**

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of data. We used Shapiro-Wilk test to assess whether the data showed normal distribution or not. Homogeneity of variance was evaluated by Levene test. We used Mann-Whitney U test when comparing independent two groups according to quantitative data, Kruskal-Wallis for comparison of more than 2 groups. In comparison of categorical variables, each other, Pearson Chi-Square test was used. To analyze the correlations of variables with each other, Spearman’s correlation(r) analysis was used. To determine the risk groups for parameters affecting the development of NODAT according to posttransplant 1st month FBG, we used univariate logistic regression analysis. Multivariate test was not applicable. Odds Ratio (OR) was used with 95% confidence intervals (CI) to show that risk groups had how higher risk than the other subjects. Quantitative variables
were defined as mean (X) ± standard deviation (SD) in the tables. Categorical variables were demonstrated as number (n) and percent (%), and p value of <0.05 was accepted as statistically significant.

Results

A total of 91 patients undergoing LTx due to ALF were analyzed in our study, mean age was 33.48(±13.35), and 52.7%(n=48) of the patients was female. The etiology of ALF was BCS in 3(3.29%) patients, acute viral hepatitis in 38(41.75%), drug or toxin-related in 21(23.07%), and other/unknown causes in 29(31.86%) patients.

11(12.08%) patients died in the 1st week, 28(30.76%) in the 1st month, 36 (39.56%) in 3 months, and 43(47.25%) in 12 months of LTx. The ratio of prediabetes and NODAT in survivors of LTx was 23.07% and 67.03% on the 1st day, 28.75% and 58.75% on the 1st week, 36.5% and 26.98% on the 1st month, 32.72% and 14.54% on 3rd month, and 20.83% and 8.3% on 12th month. If the patients were grouped according to FBG on 1st month; pretransplant RBG was significantly higher in group 3 than in group 2 (p=0.041) or in group 1 (p=0.022); 3rd month FBG was significantly higher in group 3 than in group 1 (p=0.018); 12th month FBG was significantly higher in group 2(p=0.037) or in group 3(p=0.006) than in group 1. Age, gender, body weight, BMI, thyroid function tests, and donor FBG were similar in all FBG groups on 1st month (p>0.05).

Table 1. Comparison of demographic, clinical and laboratory parameters according to the 1st month FBG.
|                | 1st month FBG Groups |                |                |                |                |
|----------------|----------------------|----------------|----------------|----------------|----------------|
|                | Group 1 (n=23)       | Group 2 (n=23) | Group 3 (n=17) | Total (n=63)   | p value        |
| **Age**        | 29.43(8.46)          | 34.39(16.18)   | 37.71(13.73)   | 33.48(13.35)   | 0.223          |
| **Body weight**| 70.96(8.37)          | 73.17(10.27)   | 74.14(11.72)   | 72.63(9.97)    | 0.528          |
| **BMI**        | 25.58(2.07)          | 25.75(2.69)    | 26.32(2.47)    | 25.84(2.40)    | 0.556          |
| **TSH**        | 1.25(0.63)           | 1.08(0.87)     | 1.28(1.13)     | 1.19(0.87)     | 0.329          |
| **fT4**        | 1.07(0.18)           | 1.11(0.18)     | 1.09(0.18)     | 1.09(0.17)     | 0.703          |
| **fT3**        | 3.18(0.37)           | 3.01(0.61)     | 3.11(0.65)     | 3.10(0.54)     | 0.737          |
| **Donor FBG**  | 105.43(15.63)        | 104.69(18.49)  | 116.80(25.58)  | 108.96(20.70)  | 0.409          |
| **Pretransplant RBG** | 92.52(36.20)       | 98.43(29.60)   | 128.53(56.59)  | 104.40(42.75)  | 0.044*+        |
| **1st day FBG**| 182.22(92.60)        | 174.70(54.62)  | 179.59(80.94)  | 178.76(76.18)  | 0.888          |
| **1st week FBG**| 137.83(50.51)       | 151.91(47.06)  | 145.41(33.88)  | 145.02(44.99)  | 0.547          |
| **1st month FBG** | 83.83(73.32)        | 111.39(8.28)   | 161.29(28.89)  | 114.79(34.81)  | 0.00           |
| **3rd month FBG** | 95.36(23.16)        | 111.0(28.13)   | 115.67(38.42)  | 105.76(29.65)  | 0.038**        |
| **12th month FBG** | 89.29(7.95)         | 98.5(16.83)    | 107.22(20.79)  | 96.10(15.80)   | 0.011+++***    |
| Gender(female/male) | 12/11               | 10/13          | 9/8            | 31/32          | 0.787          |

*p=0.022(group1-3), +p=0.041(group2-3), **p=0.018(group1-3), ++p=0.037(group1-2),

***p=0.006(group1-3)

According to the analysis of FBG on 12th month of LTx among survivors; 3 patients had persistent NODAT; NODAT changed to prediabetes in 1 patient and to normal FBG in 5 patients; prediabetes persisted in 7 patients, and changed to normal FBG in 10 patients or to NODAT in 1 patient; normal FBG persisted in 19 patients and changed to prediabetes in 2 patients.

Pretransplant hypoglycemia and hyperglycemia were found in 7(7.6%) and 5(5.4%) patients, respectively. There were no significant clinical pretransplant or posttransplant variable predicting the development of NODAT according to 1st day FBG (not demonstrated on the table). There were no significant clinical pretransplant or posttransplant variable predicting the development of NODAT according to 1st month FBG, with the exception of pretransplant hyperglycemia. Hyperglycemia detected by pretransplant RBG was found as a positive predictor for NODAT, and the presence of hyperglycemia increased the risk of development of NODAT on 1st month as 4.065 times (p=0.018). Low free T4, or low free T3 was detected in 3 patients, but none of the patients had low free T4 and T3 at the same time. A total of 14 patients (15.38%) had pretransplant subclinical thyrotoxicosis.
Table 2. Pretransplant and posttransplant factors affecting the development of NODAT according to the 1st month FBG.

| Variables                        | Univariate OR (95% CI) | p value |
|----------------------------------|------------------------|---------|
| **Pretransplant**                |                        |         |
| Age (<40/≥40)                    | 1.964 (0.582-6.629)    | 0.273   |
| Gender (female/male)             | 0.815 (0.267-2.483)    | 0.718   |
| BMI (<30/≥30)                    | 2.813 (0.166-47.65)    | 0.456   |
| Etiology (other/acute viral hepatitis) | 0.764 (0.248-2.354)    | 0.638   |
| Antiviral medication             |                        |         |
| (absence/presence)               | 1.093 (0.191-6.249)    | 0.920   |
| Subclinical hyptoxosisis         | 2.000 (0.487-8.211)    | 0.330   |
| (absence/presence)               |                        |         |
| Hypoglycemia (<54/≥54)           | 0.712 (0.605-0.837)    | 0.209   |
| Hyperglycemia (<70/≥70)          | 3.368 (0.389-29.18)    | 0.247   |
| Donor type (cadavr/living)       |                        |         |
| (absence/presence)               | 0.246 (0.158-0.382)    | 0.018   |
| Common infection                 |                        |         |
| (absence/presence)               | 4.000 (0.811-19.71)    | 0.073   |
| Surgical complication            |                        |         |
| (absence/presence)               | 1.077 (0.287-4.043)    | 0.913   |

Pretransplant RBG was positively correlated with 1st month FBG (p=0.014) and 3rd month FBG (p=0.043).

Table 3. Correlation of clinical and laboratory parameters.

| Variables | Age | Weight | Height | BMI | TSH | fT4 | fT3 | Pretransplant RBG | Donor FBG |
|-----------|-----|--------|--------|-----|-----|-----|-----|-------------------|-----------|
| Age       | 1.000 | 0.244  | 0.138  | 0.214 | 0.249 | -0.119 | -0.187 | 0.093 | 0.084 |
|           | (0.020) | (0.192) | (0.041) | (0.017) | (0.017) | (0.263) | (0.076) | (0.379) | (0.527) |
| Weight    | 0.244 | 1.000  | 0.668  | 0.713  | 0.092  | -0.112 | -0.025 | 0.075 | 0.412 |
|           | (0.020) | (0.00)  | (0.385) | (0.290) | (0.815) | (0.018) | (0.018) | (0.482) | (0.001) |
| Height    | 0.138 | 0.668  | 1.000  | 0.048  | 0.036  | 0.036  | -0.054 | -0.143 | 0.372 |
|           | (0.192) | (0.00)  | (0.654) | (0.732) | (0.732) | (0.609) | (0.004) | (0.177) | (0.004) |
| BMI       | 0.214 | 0.713  | 0.048  | 1.000  | 0.088  | -0.179 | 0.046  | 0.201 | 0.205 |
|           | (0.041) | (0.654) | (0.409) | (0.090) | (0.664) | (0.664) | (0.664) | (0.056) | (0.120) |
| TSH       | 0.249 | 0.092  | 0.036  | 0.088  | 1.000  | -0.130 | 0.163  | 0.088 | 0.063 |
|           | (0.017) | (0.385) | (0.732) | (0.219) | (0.124) | (0.407) | (0.635) | (0.407) | (0.635) |
| fT4       | -0.119 | -0.112 | 0.036  | -0.179 | -0.130 | 1.000  | -0.106 | -0.158 | -0.104 |
|           | (0.263) | (0.290) | (0.732) | (0.219) | (0.315) | (0.134) | (0.431) | (0.134) | (0.431) |
| fT3       | -0.187 | -0.025 | -0.054 | 0.046  | 0.163  | -0.106 | 1.000  | 0.109 | 0.224 |
|           | (0.076) | (0.815) | (0.609) | (0.664) | (0.124) | (0.315) | (0.124) | (0.315) | (0.124) |
| Pretransplant RBG | 0.093 | 0.075  | -0.143 | 0.201  | 0.088  | -0.158 | 0.109  | 1.000 | 0.202 |
| Donor FBG | (0.379) | (0.482) | (0.177) | (0.056) | (0.407) | (0.134) | (0.305) | (0.125) | (0.125) |
Discussion

We detected that the frequency of NODAT was 70% on 1st day, decreased progressively during follow-up, and it was detected in a minority of survivors on 12th month. Those without diabetes on the 1st month had almost stable normoglycemia on 12th month. We showed that pretransplant hyperglycemia increased the risk of NODAT by 4 times, but pretransplant hypoglycemia was not a predictor for NODAT.

Several pretransplant (age, family history of diabetes, obesity, prediabetes, hypertension, dyslipidemia, HCV infection) and posttransplant (immunosuppressive drugs such as calcineurin inhibitors, tacrolimus, cyclosporine, glucocorticoids, and CMV infection, cytokines or acute rejection) risk factors had been shown to be risk factor for post-transplant diabetes mellitus [19-28]. Some studies investigated these risk factors in specific population undergoing LTx [7,29,30]. However, in these studies, the indication of LTx consisted of both acute and chronic liver failure. There is no report that examine the development of NODAT only in the patients with ALF in particular. We analyzed the possible predictors of NODAT in the patients undergoing LTx due to ALF.

In ALF, hypoglycemia may be observed due to depleted glycogen stores, and a defect in glycogenolysis and gluconeogenesis [31]. Increased level of serum insulin may also contribute to the development of hypoglycemia in ALF [32-34]. The frequency of hypoglycemia was shown as high as 45% in this patient population [14-16]. We proposed that preoperative catabolic state contributing hypoglycemia might continue after LTx, and hence, might blunt possible posttransplant hyperglycemia in the patients with ALF. However, we found that preoperative hypoglycemia was not associated with
posttransplant DM. The frequency of hypoglycemia was 7.6% in our study and lesser than previous studies. However, we did not analyze all the patients admitted to our clinics with ALF, but we evaluated only the patients who underwent LTx due to ALF. We analyzed the predictors of NODAT according to FBG on the 1st month, and the mortality rate on the 1st month was 30.76%. The mortality rate was higher in the patients having pretransplant hypoglycemia than in the rest of the group (42.85 vs 29.76%). Therefore, the possible effect of pretransplant hypoglycemia on the development of NODAT might be underestimated. Together with this, analysis the 1st day FBG also showed that pretransplant hypoglycemia was not a significant predictor for the development of NODAT. Multicenter studies including a large population will clearly identify this issue.

Perioperative hyperglycemia was known as a risk factor for the development of NODAT [20,35]. In one study, transplant candidates with impaired glucose tolerance which was detected by glucose load were found to have an increased risk for posttransplant diabetes [36]. We showed that pretransplant hyperglycemia increased NODAT by approximately 4-fold. However, we could not perform oral glucose tolerance test because of unstable clinical condition. We evaluated preoperative glycemic status only by random blood glucose measurement. Independent of subgroups, pretransplant RBG was positively correlated with 1st or 3rd month FBG. Moreover, none of the patients having normal FBG on the 1st month did develop NODAT until 12th month. Hence, our findings suggested that pre- and post-transplant glycemic management is so important to prevent the development of NODAT at each period of the follow-up. It should be kept in mind that constitution of stable pretransplant glucose level in such a patient with ALF might be complicated.
Timing of the test for diabetes mellitus may affect the diagnosis of NODAT and hence the frequency of NODAT in transplant patients [2]. Perioperative stress may result in acute postoperative hyperglycemia. The effect of immunosuppressive drugs on glycemic status in the postoperative period may alter during the follow-up. Spontaneous remission may be observed in some patients with NODAT, especially after tapering dose of immunosuppressive drugs [37]. In some studies, analyzing renal transplant patients, NODAT was divided as early-onset, late-onset or temporary [38]. It may be thought that evaluation of post-transplant diabetes mellitus would be done under more stable clinical conditions. If rejection or surgical complications are not observed, most of the patients recovered from transplantation at the end of the 1st month [2]. Based on these reports, we evaluated and analyzed the predictors of NODAT which was diagnosed according to the 1st month FBG. We found the frequency of NODAT as 67.03% on the 1st day, 58.75% on the 1st week, 26.98% on the 1st month. So, our findings suggested the temporary alteration of NODAT. NODAT was detected in 8.3% among the survivors on 12th month. None of the patients having normal FBG on the 1st month did develop NODAT until 12th month; therefore, normoglycemia on the 1st month might point stable FBG during follow-up. We may say that if posttransplant normoglycemia is constituted in the early postoperative period, it will be stable during the follow-up. We measured only FBG after LTx; however, we could not perform glucose load or HbA1c in our study.

Pretransplant obesity or higher age, or gender were defined as risk factors for the development of NODAT [2]. Our findings showed that obesity, gender or older age (>40) were not as significant predictors for NODAT. In one study, posttransplant 12th month BMI
was also shown as an important factor for NODAT after LTx [7]. However, we could not analyze posttransplant BMI level of the patients. Sick euthyroid syndrome was frequently observed in chronic liver disease, and free T3 level was shown to be corrected after LTx in several studies [30,39]. In one study, free T3 was significantly lower in the patients with HBV related acute-on-chronic liver failure than in chronic HBV infection [40]. Systematic analysis of thyroid function tests in ALF is limited in the literature. Anastasiou et al. investigated thyroid function in ALF, and showed that the patients who recovered from ALF had higher TSH, total T4 and T3 levels than the patients undergoing LTx or died from ALF [41]. We showed that subclinical thyrotoxicosis was found in 15.38% of the patients, but according to 1st day or 1st month FBG, it was not a significant predictor for NODAT. We did not analyze the association between thyroid function and mortality; however, 8 patients with pretransplant subclinical thyrotoxicosis died in 1st month of LTx.

**Strength and Limitations**

There is no report that examine the development of NODAT only in the patients with ALF in particular. We analyzed the possible predictors of NODAT only in the patients undergoing LTx due to ALF. We did not analyze the patients with ALF whom LTx was unnecessary or unavailable, but we evaluated only the patients who underwent LTx due to ALF. So, the frequency of hypoglycemia, or the frequency of ALF due to acetaminophen were not predictable. We could not perform oral glucose tolerance test or HbA1c measurement because of unstable pretransplant clinical condition, we evaluated pretransplant glycemic status only by random blood glucose measurement. Based on the reports, we evaluated and analyzed the predictors of NODAT which was diagnosed according to the 1st month FBG. Our study was designed as a retrospective manner,
because prospective study might be difficult in such a clinical condition of ALF. Further clinical studies analyzing the development of NODAT in a large cohort of patients with LTx for a longer period will clarify the unexplained issues.

Conclusions

Our findings suggested that the frequency of NODAT was 70% on 1st day, decreased progressively during follow-up. The patient without NODAT on the 1st month had almost stable normoglycemia on 12th month. Pretransplant hyperglycemia increased the risk of NODAT by 4 times, but pretransplant hypoglycemia was not a significant predictor for NODAT. The indication of LTx consisted both of acute and chronic liver failure in the studies regarding NODAT developed after LTx; however, we analyzed the possible predictors of NODAT only in the patients undergoing LTx due to ALF. We recommend that perioperative glycemic regulation should be maintained to prevent the development of or to manage NODAT during the follow-up. It should be kept in mind that constitution of stable pretransplant glucose level in such a patient with ALF might be complicated. Multicenter studies analyzing a large cohort will give additional information about the predictors of NODAT after LTx.

Declarations

ETHICAL STATEMENT AND DISCLOSURE

Compliance with ethical standards: Our study was designed as retrospective manner, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Conflict of interest: All authors declare that they have no conflict of interest.
Ethical approval: Our study was approved by the Ethics Committee of Inonu University (Malatya Clinical Researches Ethic Committee, approval date: 04 January 2017, approval number: 2017/11)

Informed consent: Due to the retrospective design of the study and the use of already available data, written informed consent was unavailable.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ömercan Topaloğlu, Muhammet Cengiz, Ayşe Cengiz, Bahri Evren, Saim Yoloğlu, Sezai Yılmaz, İbrahim Şahin. The first draft of the manuscript was written by Ömercan Topaloğlu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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