ORIGINAL ARTICLE

# Metabolic syndrome after a liver transplantation in an Asian population

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## Abstract

**Background:** With improvements in patient survival after a liver transplantation (LT), long-term sequelae such as metabolic syndrome (MS) have become increasingly common. This study aims to characterize the prevalence, associations and long-term outcomes of post-LTMS and its components in an Asian population.

**Methods:** A retrospective review of all adult patients who underwent LT at the National University Health System Singapore between December 1996 and May 2012 was performed. MS was defined using the Adult Treatment Panel (ATP) III criteria modified for an Asian population.

**Results:** The median age of this cohort of 90 patients was 50.0 (16.0–67.0) years, with a median follow-up duration of 60.0 (7.0–192.0) months. The prevalence of post-LTMS was 35.6%, diabetes mellitus (DM) 51.1%, hypertension 60.0%, obesity 26.7% and dyslipidaemia 46.7%. On univariate analysis, factors significantly associated with post-LT MS include female gender ($P = 0.066$), pre-LT respiratory comorbidities ($P = 0.038$), pre-LT obesity ($P = 0.014$), pre-LTDM ($P < 0.001$), pre-LT hypertension ($P = 0.039$), pre-LTMS ($P < 0.001$), prednisolone use ≥24 months ($P = 0.005$) and mycophenolate mofetil use ≥24 months ($P = 0.035$). On multivariate analysis, independent associations of post-LT MS were pre-LTDM ($P = 0.011$) and pre-LTMS ($P = 0.024$). There was no difference in long-term survival of patients with and without post-LTMS ($P = 0.425$).

**Conclusion:** In conclusion, pre-LT components of the MS and the use of certain immunosuppressants are related to developing post-LTMS.

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## Introduction

Liver transplantation (LT) has seen vast improvements in surgical techniques and immunosuppression over the past four decades since the first successful human liver transplant performed in 1967.[1] LT is now considered a definitive treatment for patients with end-stage liver disease and selected cases of hepatocellular carcinoma.[2–4] With LT achieving 5-year survival rates in excess of 70% with modern management,[3–5] long-term sequelae of liver transplantation and lifelong immunosuppression have assumed greater clinical importance.

Post-LT metabolic syndrome (MS) has emerged as an increasingly prevalent condition amongst post-LT patients.[5–7] With the established association between MS and cardiovascular disease, it is not surprising to see an increasing proportion of mortality and graft loss post-LT related to cardiovascular disease.[5]

Many studies have looked at post-LT MS in Western populations[8–12] but the applicability of such findings to an Asian population remains unclear. There are differences between body mass index (BMI), the percentage of body fat and health risks when comparing European and Asian populations, according to the World Health Organization (WHO) expert consultation.[13] As such, this study aims to characterize the prevalence, predictive factors and long-term outcomes of post-LT MS and its components in an Asian population, transplanted at an Asian centre.

 

## Methods

A retrospective chart review of all adult patients who underwent LT and are on long-term follow-up at the National University Health System, Singapore from December 1996 to May 2012 was conducted. Patients with < 6 months of follow-up duration at the time of the study were excluded. There was a total of 90 patients included in the study.

The metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria,[14] with a modification to the abdominal obesity criteria (Table 1). As proposed by a consensus statement from the International Diabetes Federation, a body mass index (BMI) of 30 kg/m$^2$ in European populations can be used as a surrogate indication of a waist circumference exceeding the threshold required to fulfill the abdominal obesity criteria.[15] In order to better tailor the diagnostic criteria for the MS to our study population, we used the corresponding Asian BMI cut-off of 27.5 kg/m$^2$ instead, in accordance with a 2004 WHO expert consultation.[13]

In addition, components of MS, namely diabetes mellitus (DM), hypertension, dyslipidemia and obesity, were studied individually. DM, hypertension and dyslipidemia were considered present if a medical diagnosis was recorded, or if the patient was on pharmacological therapy for any of these conditions. Details pertaining to the onset and progression of these chronic conditions were also captured in the data collection process. Obesity was defined by a BMI of 27.5 kg/m$^2$ or greater.[13] Information related to morbidity and survival of the patients with and without MS was documented, in particular, those related to cardiovascular events that may be related to MS.

Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). For univariate analyses, continuous variables were analysed using the Mann–Whitney *U*-test whereas categorical variables were analysed using either the chi-square or Fisher's exact test. Subsequent multivariate analyses were performed using logistic regression. Kaplan–Meier curves were created for survival analysis in this study. A level of significance of 5% was used.

## Results

The median age in our study population was 50 (16–67) years with a male preponderance ($n$ = 69, 76.7%) and predominant Chinese ethnicity ($n$ = 69, 76.7%). The median duration of follow-up was 60 (7–192) months. Hepatitis B cirrhosis ($n$ = 45, 50.0%) comprised the majority of the underlying liver diseases in our study population, followed by hepatitis C cirrhosis ($n$ = 11, 12.2%) and acute liver failure ($n$ = 11, 12.2%). Additionally, nearly half the patients had hepatocellular carcinoma (HCC) at the time of LT ($n$ = 42, 46.7%). Of the 90 patients we studied, 77 (85.6%) were deceased-donor liver transplantations.

The prevalence of post-LT MS in our study was 35.6% ($n$ = 32), nearly double the percentage of patients with MS in the pre-LT period ($n$ = 17, 18.9%) ($P$ = 0.001). There were 17 new patients who developed MS post-LT (Table 2). Of the 17 patients with pre-existing MS, two had a resolution of MS post-LT. Both of them had hepatitis B cirrhosis with pre-existing hypertension. Incidentally, the resolution of MS was as a result of a decrease in BMI in one patient and resolution of the high-density lipoprotein (HDL) level in the other.

On univariate analysis, factors found to be significantly associated with post-LT MS include the presence of pre-LT respiratory comorbidities, pre-LT components of the metabolic syndrome such as DM, hypertension and obesity, pre-LT MS itself and the use of immunosuppressants prednisolone or mycophenolate mofetil for 24 months or more (Table 3). Subsequent multivariate analysis revealed pre-LT DM and pre-LT MS to each be independently associated with post-LT MS (Table 3).

There were 46 (51.1%) post-LT DM, 54 (60.0%) post-LT hypertension, 42 (46.7%) post-LT dyslipidemia and 24 (26.7%) post-LT obesity cases, respectively. This reflects a 16.7% increase in DM in the post-LT population ($P$ = 0.001), and an almost three-fold increase in post-LT hypertension (22.2% pre-LT to 60.0% post-LT, $P$ < 0.001). The percentage of patients with pre-LT and post-LT dyslipidaemia were comparable ($P$ = 0.848). All in all, with the exception of obesity, the prevalence of MS and its components increased after LT (Table 2).

**Table 1** Modified NCEP ATP III criteria for metabolic syndrome

| Risk factors | Defining level |
|---|---|
| (1) Abdominal obesity | ≥27.5 kg/m$^2$ |
| (2) Triglyceride (TG) | ≥150 mg/dl or pharmacologic treatment |
| (3) High-density lipoprotein (HDL) | <40 mg/dl (male), <50 mg/dl (female) or pharmacologic treatment |
| (4) Blood pressure (BP) | ≥130/85 mmHg or pharmacologic treatment |
| (5) Fasting glucose | ≥110 mg/dl or pharmacologic treatment |

The presence of ≥ 3 risk factors is required to diagnose metabolic syndrome.

**Table 2** The prevalence of metabolic syndrome and its components pre- and post-liver transplantation (LT)

| Metabolic syndrome component | Pre-LT (%) | Post-LT (%) | *P*-value* |
|---|---|---|---|
| Diabetes mellitus | 31 (34.4) | 46 (51.1) | 0.001 |
| Hypertension | 20 (22.2) | 54 (60.0) | <0.001 |
| Dyslipidemia | 40 (44.4) | 42 (46.7) | 0.878 |
| Obesity | 28 (31.1) | 24 (26.7) | 0.481 |
| Metabolic syndrome | 17 (18.9) | 32 (35.6) | 0.001 |

*Statistical significance of $P$ < 0.05.