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RESEARCH ARTICLE

POSTOPERATIVE PAIN INCIDENCE, ASSESSMENT AND ITS ASSOCIATION WITH POST TRANSPLANT OUTCOME IN LIVER TRANSPLANTATION

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ABSTRACT

Introduction Postoperative pain (POP) represents a major challenge in the management of surgical patients, as it is highly common after major surgeries and is associated with increased morbidity and mortality. POP and its impact on patients who underwent liver transplantation (LT) is poorly understood. **Aim** This study was undertaken to investigate the incidence, assessment of POP, and clinical outcomes of patients with high level of postoperative pain in LT. **Materials and methods** After IRB approval, adult LT patients between March 2013 and September 2015 at our center were retrospectively reviewed. All patients who were extubated in the first week following LT were included. Pain score (0 to 10) during the first seven days post-extubation was assessed by numerical rating scale and recorded. Patients were divided into two groups: postoperative low to moderate pain score (PLMPS) reported pain score from (0-6) and postoperative high pain score (PHPS) from (7-10). The two groups were compared using univariate analysis and independent risk factors were identified by multivariate logistic regression. Of 424 patients who underwent LT during this period, 272 were extubated within the first postoperative week and were included in the analysis. **Results** A total of 114 (41.9%) patients reported pain score at 7 or higher during 7 days following extubation and 158 patients (58.1%) reported pain score "between 0 to 6" during the same period. There were no significant differences regarding to age, gender, MELD score, surgery time, intraoperative blood transfusion, vasopressor use and renal replacement therapy between the PLMPS and PHPS groups. However, patients in the PHPS group had a higher dose of hydromorphone (6.2±7.1 vs. 3.4±4.3, p=0.001), oral morphine equivalent (233.9±302.7 vs 132.6±309.8, p=0.008), and longer hospital stay after LT compared with those in the PLMPS group (44.2±46.3 days vs 30.7± 26.6, p=0.006). Using multivariate logistic regression analysis, PHPS was independent risk factor for prolonged (>30 days) hospital stay after LT (OR 2.0 95% CI 1.04-3.83, p=0.04). Other independent risk factors for prolonged hospital stay after LT include preoperative encephalopathy, renal replacement therapy, and graft failure. **Conclusion** PHPS was reported to affect 41.9% of adult LT patients. Patients with PHPS had high doses of hydromorphone, oral morphine equivalent andprolonged hospital stay after LT than patients with PLMPS. Out findings, highlight the importance of pain incidence, assessment and management after LT. **Abbreviations:** POP, postoperative pain; OLT, orthotopic liver transplantation; LT, liver transplantation; PHPS, postoperative high pain score; PLMPS, postoperative low to moderate pain score; OME, oral morphine equivalent; CI, confidence interval; OR, odds ratio; MELD, model for end-stage liver disease; UCLA, University of California, Los Angeles.

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INTRODUCTION

Postoperative pain (POP) represents a major challenge in the management of surgical patients, as it is highly common among patients (Pan, 2006). POP is harmful in itself and play an important rule on patient satisfaction, mobilization after surgery, and the length of hospital stay (Kehlet, 2001).

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POP not only affects the patient satisfaction and its operative outcome but also is associated with the development of hyperventilation, decrease in alveolar ventilation, tachycardia, insomnia and poor wound healing, which directly may affect the operative outcomes (Breivik, 1998; Breivik, 2008 and Carr, 1999). Pain after surgery that last more than 1 month occurs in 10% to 50% of individuals after major procedures, and 2% to 10% of these patients exposed to the risk of severe chronic pain (Grosu, 2011).The intensity of POP also increases the chance of developing persistent postsurgical pain (Kehlet, 2006) and contributes to increased postoperative morbidity and mortality (Kehlet, 2002).

Other important factors should be consider on predicting the intensity of postoperative pain with its analgesic requirements as preexisting pain, age, type of surgery, anxiety, and pain catastrophizing (Sommer, 2010). This is why adequate pain management is an essential component in the provision of quality health –care planning as it helps to diminish postoperative complications, such as cardiovascular or respiratory problems, or postoperative delirium (Kehlet, 2001; Carney, 2002 and Hall, 2002). Liver transplant (LT) is a life-saving surgery for patients with end-stage liver diseases (Martin, 2014; European Association for the Study of the Liver, 2015). To date, the incidence of POP and its impact on patients who underwent LT is poorly understood, however this type of surgery is among the major abdominal operations in terms of duration and stress for the patient (Eisenach, 1989). It was shown by Donovan *et al* (Donovan, 1997), that the neuropeptide modulating pain and met-enkephalin, was significantly elevated in liver transplant patients in response to pain when compared with the control population, leading to decreased postoperative analgesic requirements after OLT. Patients with liver disease have also characteristic features of central and peripheral analgesic effects with increased plasma levels of endogenous opioid peptides (Hortnagl, 1984). Postoperative pain relief has a good benefit that aims to improve pulmonary function (Ballantyne, 1998), early mobilization after surgery and early return of bowel function (Ahn, 1988). The aim of this retrospective, cohort study, were: (1) to determine the incidence and assessment of POP in adult LT patients; and (2) to identify the potential clinical outcomes that related to patients with high level of postoperative pain.

MATERIALS AND METHODS

Study population: After obtaining approval of institutional review board (IRB) of the University of California, Los Angeles (UCLA), adult (age > 18 years) LT patients between March 2013 and September 2015 at our center were retrospectively reviewed. A total of 424 patients underwent LT during this period. Pediatric patients whose age < 18 years (n=41) were excluded from the study. Of 383 adult patients underwent LT, 111 patients were excluded, leaving 272 patients for analysis as shown in fig 1. Inclusion criteria were as follows: (1) adult patients (age > 18 years); (2) patients who were only extubated in the first week postoperative following LT (n=272). Exclusion criteria were: (1) pediatric patients whose age < 18 years (n=41); (2) intubated patients in the first week postoperative (n=59); (3) recombined transplantation occurrence in the same period (n= 45); and (4) re-transplantation occurrence in the same period (n=7). Thus, 272 of the 424 patients were included (64.1%). We excluded re-transplantation and recombined transplantation surgeries as it affects the pain scores during the first week post-extubation after LT. Patient demographic, preoperative and intraoperative data were retrospectively collected. Data related to postoperative variables and outcome that were specific to the interest of this study were also collected retrospectively.POP was defined as acute onset of pain that occur during the first week post-extubation after LT. Pain was assessed as a dependent variable in its intensity by a numeric rating scale (NRS) which has been suggested to be the most useful clinical index of pain intensity among postoperative patients (Jensen, 1989). The NRS is an 11-point numerical scale ranging from 0 to 10, where 0 indicates no pain and 10 indicates the worst possible pain. According to previous publications, pain in this scale was classified as mild with a score of 1–3, moderate with scores of 4–6, and severe with scores of 7–10 (Taillefer, 2006; Lahtinen, 2006). We reported pain scores every four hours for each day. The highest pain score (0-10) for each day were recorded during the first week post-extubation after LT. Abdominal right upper quadrant pain was the main site that we reported. Patients were divided into two groups. Patients who exposed only from low to moderate pain score together (score 0-6) during this period were named as Postoperative Low to Moderate Pain Score (PLMPS) group and patients who exposed to high pain score (score 7-10) during the same period were named as Postoperative High Pain Score (PHPS) group. Treatments of POP included opioids drugs as fentanyl, morphine, hydromorphone and oxycodone were converted into oral morphine equivalents (OME), so to compare pain treatment between the two groups.

Analgesics: Use of postoperative opioid analgesics, including fentanyl, morphine, hydromorphone and oxycodone was recorded. The route of administration of these drugs were taken intravenous (infusion or bolus), except oxycodone taken by tablets. Analgesic drugs are expressed in milligram except fentanyl in mike (mcg). Opioid use was calculated, according to published equianalgesic opioid doses as OME (McPherson, 2010), and summed to obtain an index of daily opioid intake for the first week post-extubation after LT (Caraceni, 2012). Doses are expressed as milligram opioid equivalent per kilogram of body weight, to normalize opioid dose equivalents between patients (Rockville, 1992). Liver parameters included liver enzymes as Aspartate transaminase (AST), Alanine transaminase (ALT) and Alkaline phosphatase, in addition to platelets count (PLT) and international normalized ratio (INR). All of them were defined as the highest value recorded for each day during the first week postoperative after LT. Their normal serum level were as follows: (1) AST (7-36 U/L), (2) ALT (4-45 U/L), Alkaline phosphatase (31-103 U/L), INR (1.0-1.1), and PLT (144-398 x10-9/UL). We analyzed all of the liver parameters at the same period.Outcomes measures included opioids measures as discussed before, prolonged hospital stay and graft failure. We defined prolonged hospital stay as hospitalization for greater than 30 consecutive days following liver transplantation. We determined graft failure by either re-transplantation occurrence or recipient mortality during the first month after LT.

Statistical analysis: Categorical variables were compared using chi-square test and presented as percentages. Continuous variables were analyzed using the Student t-test and presented as mean standard deviation or in case of data without normal distribution, Mann-Whitney U-test was used. Univariate and multivariate analysis were used to evaluate risk factors for PHPS and prolonged hospital stay. The potentially significant variables ($P<0.1$) were selected for multivariate analysis. The multivariate analysis was performed by logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) and p values were reported. Statistical significance was considered as p value <0.05 (two sided).The association between the PHPS and opioid analgesics intake was assessed during the first week post-extubation after LT using Pearson correlation. In addition, the association between the liver parameters in first week postoperatively after LT and the occurrence of PHPS was assessed using the same test. We performed all statistical analyses using IBM SPSS version 24 (IBM, Armonk, NY).

RESULTS

A total of 424 adult patients underwent LT at our medical center in UCLA between March 2013 and September 2015. After exclusion of 152 patients, 272 patients were included inthe study. The mean and median age was 55.1 and 58.0, ranging from 18 to 75 years old. Male patients covered 60.3% of the total. The mean age in male and female patients was 56.0 and 54.0. Both White and Hispanic race comprises a same majority of recipients (36.5%), followed by Asian (10.7%) and African American (5.7%). The major etiology of end stage liver disease was hepatitis

C (40.8%), followed by alcoholic cirrhosis (13.6%), biliary cirrhosis (9.6%) and nonalcoholic steatohepatitis (8.8%).Pain distribution among the patients was recorded during the first week post-extubation after LT, according to the highest pain score for each day, as in fig 2. It showed that 90 patients (33.1%) reported pain score at 6, which was the highest percentage among patients, followed by 44 patients (16.2%) at 7, 35 patients (12.9%) at 8, 28 patients (10.3%) at 5, 20 patients (7.4%) at both 10 and 0, 16 patients (5.9%) at 9, 6 patients (2.2%) at 2,3,4 and one patient (0.4%) at 1. A total of 114 patients (41.9%) reported pain score at 7 or higher PHPS during first week following extubation and 158 patients (58.1%) reported pain score between 0 to 6 PLMPS during the same period. The mean age of patients with PHPS was 53.7. We treated the two pain score groups with opioids analgesics drugs.Results of the univariate analyses of the studied variables among patients with PLMPS and PHPS are shown in (Tables 1, 2). There were no significant differences regarding to age, gender, model for end-stage liver disease (MELD score), surgery time, intraoperative blood transfusion, vasopressor use and renal replacement therapy between PLMPS and PHPS groups. However, PHPS had significantly a higher incidence than PLMPS group in postoperative INR (1.5±0.3 vs 1.3±0.1, p=<0.001), AST (786.8±581.0 vs 477.7±353.2, p=<0.001), ALT (636.7±509.1 vs 472.3±290.3, p=0.002), Alkaline phosphatase (157.4±84.8 vs 127.5±46.6, p=0.001) and PLT (114.9±37.0 vs 181.9±69.2, p=<0.001). Patients with PHPS was associated significantly with low urine output (282±333 vs 405±618, p=0.040) than those with PLMPS. (Table 3) showed how the PHPS group had higher doses of hydromorphone (6.2±7.1 vs 3.4±4.3, p=0.001), OME (233.9±302.7 vs 132.6±309.8, p=0.008) and prolonged hospital stay after LT compared with PLMPS group (44.2±46.3 vs 30.7± 26.6, p=0.006), (Fig 3).

A total of 34.2% in the PHPS were in hospital longer than 30 days compared with 22.2% in the PLMPS group (p=0.027). The incidence of prolonged hospital stay (>30 days) that occurred due to PHPS was 52.7% versus only 37.9% for those patients without prolonged hospital stay.Multivariate analysis showed also that patients with PHPS was independent risk factor for prolonged (>30 days) hospital stay after LT (OR 2.0, 95% CI 1.04-3.83, p=0.037) as in (Table 4). Other risk factors for prolonged hospital stay after LT included graft failure (OR 10.0, 95% CI 1.84-52.84, P=0.008), which had the highest OR, followed by renal replacement therapy (OR 4.5, 95% CI 2.23-9.07, P=<0.001), reoperations (OR 2.8, 95% CI 1.44-5.46, P=0.002), preoperative encephalopathy (OR 2.5, 95% CI 1.26-5.01, P=0.009). The positive correlations and the highest significance were found between pain score groups in the first week post-extubation after LT with both of hydromorphone dosage (r=0.225, p=0.001) and OME at the same period (r=0.245, p=<0.001). Those patients who got the highest pain scores postoperative during this period, had the highest use of opioids analgesics (Fig 4).

Pain distribution among the patients was recorded during the first week post-extubation after LT, according to the highest pain score for each day. It showed that 90 patients (33.1%) reported pain score at 6, which was the highest percentage among patients, followed by 44 patients (16.2%) at 7, 35 patients (12.9%) at 8, 28 patients (10.3%) at 5, 20 patients (7.4%) at both 10 and 0, 16 patients (5.9%) at 9, 6 patients (2.2%) at 2,3,4 and one patient (0.4%) at 1. Patients pain score vs. hydromorphone dose during the first week post-extubation after LT, r = 0.225, p = 0.001. Those patients who got the highest postoperative pain scores during this period also had the highest dose of hydromorphone drug. Patients pain score vs. OME during the first week post-extubation after LT, r = 0.245, p < 0.001. Those patients who got the highest postoperative pain scores during this period also had the highest dose of OME.

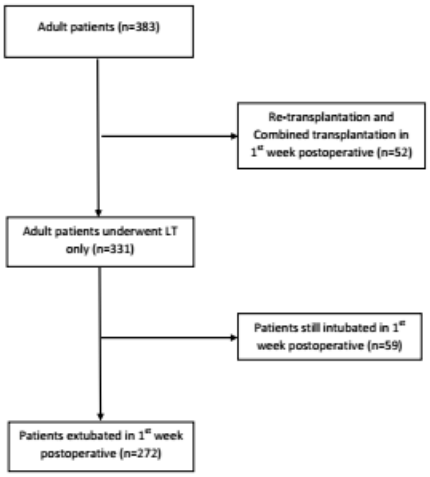

Figure 1.Flow chart. Of 383 adult patients underwent LT, 111 patients were excluded, leaving 272 patients for analysis

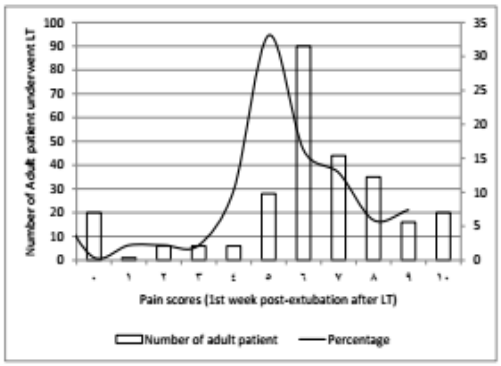

Figure 2. The pain scores ranging from (0 to 10) are on the left (Y-axis) and the number of adult patient underwent LT are on the right (X-axis)

DISCUSSION

In this retrospective cohort study, we report PHPS after LT was common. It affects 41.9% of adult patients, which are a high percentage among the study population. The reported incidence of POP in different studies and its impact on patients undergoing LT is poorly understood, however this type of surgery is among the major abdominal operations in terms of duration and stress for the patient (Eisenach *et al*., 1989). Results of the univariate analyses of the studied demographic, preoperative and intraoperative variables showed no significant differences regarding to age, gender, MELD score, surgery time, intraoperative blood transfusion, vasopressor use and renal replacement therapy between PLMPS and PHPS groups, which is also poorly reported in the past studies that related to LT field. This is may be the result of smaller sample sizes representing the groups in our study. Other studies related to major cardiac surgeries showed significant differences to age and gender according to their previous research (Watt *et al*., 2004; Lahtinen *et al*., 2006; Parry *et al*., 2010). The liver parameters in the first week postoperative after LT included AST, ALT, Alkaline phosphatase, INR and low PLT. The higher liver parameters in first week postoperative after LT, the more PHPS had occurred for patients. We could not confirm this direct correlation, as there were no studies done before about this association in LT field. However, there were studies showed that LT candidates present low platelet counts due to congested splanchnic circulation, reduced bone marrow activity and increased mechanical stress, which are not immediately reverted

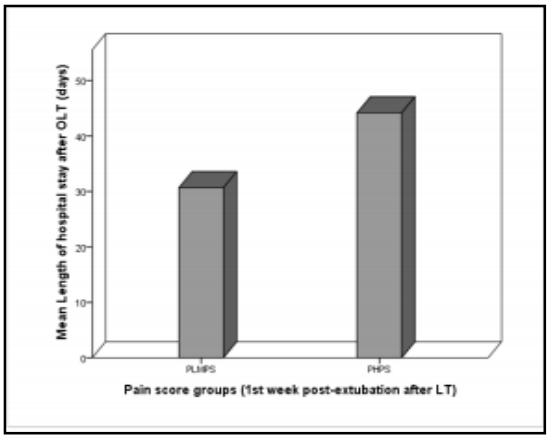

Figure 3.Graph showing the frequencyofpatients with PHPS was associated significantly with prolonged hospital stay after LT compared with PLMPS group (44.2±46.3 vs 30.7± 26.6, p=0.006)

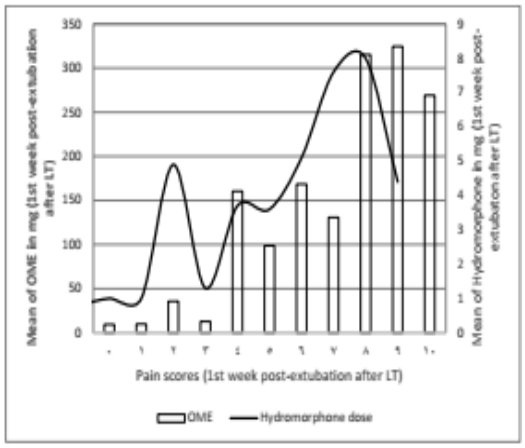

Figure 4. Pearson correlation

Table 1. Univariate analysis of demographic and preoperative variables

	PLMPS group (n=158)	PHPS group (n=114)	p-Value
Age (year)	56.2±11.7	53.7±12.9	0.103
Gender			0.234
Male (%)	100(63.3)	64(56.1)	
Female (%)	58(36.7)	50(43.9)	
Height (cm)	168.4±12.2	170.0±27.5	0.506
Weight (kg)	79.1±18.6	78.0±20.4	0.632
BMI (Kg/m2)	28.4±5.7	27.9±4.8	0.504
Race			
White (%)	30(31.6)	28(43.8)	0.118
African American (%)	6(6.3)	3(4.7)	0.663
Hispanic (%)	34(35.8)	24(37.5)	0.826
Asian (%)	16(16.8)	1(1.6)	0.002
Others (%)	9(9.5)	8(12.5)	0.545
Etiology of liver disease			
Hepatitis C (%)	64(40.5)	47(41.2)	0.905
Alcoholic cirrhosis	19(12.0)	18(15.8)	0.372
Nonalcoholic steatohepatitis (%)	17(10.8)	7(6.1)	0.185
Biliary cirrhosis cause (%)	12(7.6)	14(2.3)	0.195
Others (%)	46(29.1)	28(24.6)	0.405
Baseline hematocrit (%)	28.6±17.8	27.3±6.7	0.452
Baseline platelet	76.3±69.4	66.8±33.7	0.137
Baseline INR	3.2±10.4	2.6±4.3	0.593
Baseline creatinine (mg/ml)	1.5±1.2	1.5±1.3	0.919
Preoperative intubation (%)	35(22.6)	22(19.5)	0.539
Preoperative dialysis (%)	54(34.2)	36(31.6)	0.653
Hypertension (%)	46(29.5)	35(30.7)	0.83
Diabetes Mellitus (%)	37(23.7)	30(26.3)	0.625
Encephalopathy (%)	65(41.7)	44(38.6)	0.612
Hepatocellular carcinoma (%)	63(40.4)	44(38.6)	0.767
Ascites (>1L) (%)	57(37.0)	46(40.4)	0.597
Gastrointestinal bleeding (%)	42(26.9)	31(27.4)	0.926
MELD score	33.5±8.2	32.7±8.1	0.444

Table 2. Univariate analysis of intraoperative variables

	PLMPS group (n=158)	PHPS group (n=114)	p-Value
Surgery time (min)	566.7±103.6	563.2±140.3	0.813
Cold ischemic time (minutes)	448.7±151.2	446.2±118.9	0.935
Warm ischemic time (minutes)	51.8±12.6	53.4±15.7	0.606
Group Venovenous Bypack (%)	28(37.8)	20(30.8)	0.382
Highest Pre-reperfusion K (mmol/L)	4.6±0.8	4.5±1.0	0.324
Highest Post-reperfusion K (mmol/L)	4.4±1.3	4.7±1.0	0.035
Red blood cell (unit)	8.5±6.6	7.7±6.4	0.368
Platelets requirement (unit)	1.3±1.7	1.9±3.7	0.128
Fresh frozen plasma (unit)	10.2±9.1	8.7±7.2	0.14
Cryoprecipitate (unit)	1.4±2.5	1.0±1.3	0.119
Urine output (ml)	405±618	282±333	0.04
Continues infusion of vasopressor (%)	135(86.5)	87(79.8)	0.144
Repeated bolus vasopressor (%)	63(40.1)	44(40.0)	0.983
Reperfusion Syndrome (%)	93(58.9)	73(64.0)	0.388
Intraoperative dialysis (%)	32(20.3)	16(14.0)	0.184

Plasma and platelet transfusions have a negative correlation outcome after LT that might be associated with a lower postoperative platelet count (Chang *et al*., 2000; de Boer *et al*.,

Thrombocytopenia is associated after LT with early allograft dysfunction, early bacterial and fungal infections (before POD14), and patient mortality (Chatzinetrou *et al*., 1999)

Table 3. Univariate analysis of postoperative variables and outcomes

	PLMPS group (n=158)	PHPS group (n=114)	p-Value
INR (1st week postop.)	1.3±0.1	1.5±0.3	<0.001
AST (U/L) (1st week postop.)	477.7±353.2	786.8±581.0	<0.001
ALT (U/L) (1st week postop.)	472.3±290.3	636.7±509.1	0.002
Alkaline phosphatase (U/L) (1st week postop.)	127.5±46.6	157.4±84.8	0.001
PLT (1st week postop.)	181.9±69.2	114.9±37.0	<0.001
Renal replacement therapy (%)	65(41.4)	45(39.5)	0.75
Reoperations (1st week post-extubation) (%)	39(24.7)	34(29.8)	0.345
Fentanyl dose (mcg) (1st week post-extubation)	700.0±1185.1	705.6±869.1	0.979
Morphine dose (mg) (1st week post-extubation)	58.1±75.3	111.8±290.4	0.642
Hydromorphone dose (mg) (1st week post-extubation)	3.4±4.3	6.2±7.1	0.001
Oxycodone dose (mg) (1st week post-extubation)	79.7±140.2	117.0±114.4	0.056
Oral Morphine equivalents (mg)	132.6±309.8	233.9±302.7	0.008
Length of hospital stay after OLT	30.7±26.6	44.2±46.3	0.006
Prolonged hospital stay (>30 days after LT) (%)	35(22.2)	39(34.2)	0.027

Table 4. Multivariate analysis of Prolonged hospital stay (>30 days) (Logistic regression)

Independent risk factors	P-value	OR	95% C.I. for OR	
Graft failure	0.008	9.857	1.839	52.84
Renal Replacement Therapy	0	4.499	2.232	9.07
Reoperations	0.002	2.805	1.44	5.462
Encephalopathy	0.009	2.509	1.257	5.007
Postoperative High Pain Scores (PHPS)	0.037	1.998	1.041	3.834

AST and ALT are enzymes that involved in metabolism of amino acid, but despite ALTs are more liver-specific, ASTs present at higher concentrations in the liver (Remien *et al*., 2012). Primary non-function (PNF) and initial poor function (IPF) definitions in the early 1990s were based on high levels of transaminases as an indicator of hepatocellular lysis and hepatic damage. Olthoff *et al* (Olthoff *et al*., 2010) excluded INR and bilirubin up to postoperative day seven (POD7), considering that they might reflect the recipient pre-transplant status and not graft functionality, but AST and ALT were evaluated daily up to POD7 reflecting eventual graft injury. In this study, we found a strong correlation between the pain groups and opioid analgesics intake in the first week post-extubation after LT. It also showed a high significance in PHPS than the PLMPS group regarding to hydromorphone dose as a drug and OME as a group. Studies done before reported a similar significance in this association but with a decreased analgesic requirements compared with other types of major abdominal operations as hepatic resection surgeries and hepatocellular carcinoma patients undergoing partial hepatectomy (Chen *et al*., 2010; Moretti *et al*., 2002 . Eisenach and colleagues (Eisenach *et al*., 1989) reported that patients who underwent LT require less postoperative morphine analgesia compared with patients who underwent open cholecystectomy. Their findings were in agreement with those of other studies. They explained that this difference caused by endogenous factors rather than altered pharmacokinetics however; morphine metabolism in the absence of renal disease is unchanged after liver transplantation. This was also postulated by Donovan *et al* (Donovan *et al*. 1997) that he had reported decreased postoperative analgesic requirements in LT patients, assuming that the contributing factor was increased levels of endogenous opioid neuropeptides (e.g. methionine-enkephalin). He suggested that met-enkephalin was a more significant factor compared with substance P levels and circulating B-endorphin. Additionally, Spivey *et al* (Spivey *et al*., 1994) demonstrated that the elevation in neuropeptide modulating pain was proportionate to the stage of liver disease. The present study showed that prolonged hospital stay (>30 days) was significantly higher in the PHPS versus the PLMPS group (34.2% vs 22.2%, p=0.027). By logistic regression, PHPS group was one of the independent risk factor for prolonged hospital stay after LT. Other risk factors for prolonged hospital stay after LT included graft failure, which had the highest OR, followed by renal replacement therapy, reoperations and preoperative encephalopathy. This was different than a study reported by (Smith *et al*., 2009) Incidence of Prolonged Length of Stay (PLOS) after Orthotopic Liver Transplantation (OLT), as it demonstrated factors that associated with prolonged hospital stay included intensive care unit status at the time of OLT, OLT prior to Model for End-Stage Liver Disease implementation, in-hospital post-OLT bacterial infection, gastrointestinal bleeding, renal failure and allograft rejection. The incidence of PLOS was 13% in their cohort study with a median hospital stay of 50 days versus only 10 days for those patients without PLOS, while the incidence of prolonged hospital stay (>30 days) in our study that occurred due to PHPS was 52.7% versus only 37.9% for those patients without prolonged hospital stay. PHPS lost its significance in their multivariate analysis study. The cause of this discrepancy is not entirely clear, but can direct our study to be more focusing on the way that how postoperative pain management should be postoperative satisfied to LT patients especially the PHPS group. There are some limitations of this study. First, the study design was retrospective with many inherent shortcomings that may lead to underestimating the incidence of PHPS and failure to identify risk factors. Second, there is a possibility that certain confounding factors for PHPS or its outcomes were not included in our study. Third, the results of our study were based on data from one center only, so caution is needed when interpreting our data, as it varies from centers to centers. Although there are limitations, our study is one of the rarely studies to identify the incidence and potential outcomes of PHPS after LT and a causal relationship between PHPS and its outcomes. Therefore, our results need to be confirmed by other centers.

In conclusion, in this retrospective cohort study, PHPS was found to affect 41.9% of adult LT patients. Patients with PHPS had high doses of hydromorphone as a drug, OME as a group, and prolonged hospital stay after LT than patients with PLMPS. These findings in our study highlight the importance of pain incidence, assessment and management after LT, as it helps to reduce or prevent the adverse effects of inadequate pain control.

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