Liver transplant versus non-liver transplant patients underwent appendectomy with presumed diagnosis of acute appendicitis: Case-control study

Kemal Barış Sarıcı, M.D., Sami Akbulut, M.D., Cemalettin Koç, M.D., Adem Tuncer, M.D., Sezai Yılmaz, M.D.

Department of Surgery and Liver Transplant Institute and, İnönü University Faculty of Medicine, Malatya-Turkey

ABSTRACT

BACKGROUND: This study aims to compare liver transplant and non-liver transplant patients who underwent appendectomy with a presumed diagnosis of acute appendicitis.

METHODS: Demographic and clinicopathological features of 13 liver transplant recipients (transplant group) who underwent post-transplant appendectomy with a presumed diagnosis of acute appendicitis were compared with the features of 52 non-liver transplant patients (non-transplant group). They underwent appendectomy with a presumed diagnosis of acute appendicitis during the same time period. The transplant group was matched at random in a 1:4 ratio with the non-transplant group. While the continuous variables were compared using the Mann Whitney-U test, categorical variables were compared with Fisher’s exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS: A total of 65 patients aged between one year and 84 years were included in this study. While the age of the 52 patients (32 male and 20 female) in the non-transplant group ranged from 17 years to 84 years, the age of the 13 patients (nine male and four female) in the transplant group ranged from one year to 64 years. Statistically significant differences were noted between both groups concerning WBC (p=0.002), neutrophil (p=0.002), lymphocyte (p=0.032), platelets (p=0.032), RDW (p=0.001), CRP (p=0.009), PNR (p=0.042), WNR (p=0.03), and appendiceal length (p<0.001). The negative appendectomy rate was relatively higher in transplant than the non-transplant group but this difference was not statistically significant (30.8% vs. 21.2%; p=0.477). Perforated acute appendicitis occurred more frequently in the transplant group; however, this difference was not statistically significant (30.8% vs. 9.6%; p=0.070).

CONCLUSION: WBC and neutrophil were lower in the LT group; however, the CRP and RDW were higher in the LT group. Further, perforation and negative appendectomy rates were higher in the LT group, although this difference was not statistically significant.

Keywords: Liver recipients; acute appendicitis; Liver transplantation; negative appendectomy; perforated appendicitis.

INTRODUCTION

Acute appendicitis (AAp) is one of the most common causes of admission to emergency units, and appendectomy is one of the most frequently performed surgical procedures in the world.[1] The lifetime risk of an AAp episode is 8.6% in male and 6.7% in female patients.[2–3] Epidemiologic studies state that the risk of undergoing an appendectomy at any point in their lives in male and female patients is 12% and 23%, respectively.[1] Parameters, such as leukocyte count, neutrophil count, C-reactive protein (CRP) level, some interleukins (IL), procalcitonin level, and the findings of physical examination, used in the diagnosis of AAp depend on the extent of the host response to the inflammation in the body. Despite the contradicting findings in the literature, there is a general consensus that AAp signs and symptoms in an immunocompromised individual may differ from AAp signs and symptoms in an immunocompetent patient.[4–8] Thus, it has been sug-
gusted that transplant patients may have a higher rate of late
diagnosis and risk of fatal complications, such as perforation and
abscess formation, due to immunosuppressive therapy
received in the postoperative period.[7] The present study
aims to compare the demographic and clinicopathologic data
of the immunosuppressed liver transplant (LT) recipients who
underwent an appendectomy due to AAP to that of their
non-transplant counterparts who underwent appendectomy
during the same period. This study will provide an indirect
means of investigation of the effects of immunosuppressive
therapy on the signs and symptoms of inflammation in AAP.

MATERIALS AND METHODS

Between March 2002 and October 2019, a total of 2442 pa-
tients underwent LT in Inonu University Liver Transplant Insti-
tute, and 13 (0.53%) of these patients underwent appendec-
tomy with a presumed diagnosis of AAP after LT. This group was
defined as the LT group (n=13). A control group was created
for comparison with the transplant group, and this group was
defined as the non-LT group (n=52). The non-LT group com-
prised patients who presented to our emergency unit with
abdominal pain in the same time period and underwent ap-
pendectomy with the presumed diagnosis of AAP. Patients
with a history of corticosteroid, chemotherapeutic agent, or
other immunosuppressive drug use for any reason were not
included in the non-LT group. The LT group was matched at
random in a 1:4 ratio with the non-transplant group (G*Pow-
er 3.1.9.2 software; effect size=0.7, two-tailed, power: 81.8%,
Df:63, critical t=1.349, non-centrality parameter=2.257). To
minimize the bias risk, the non-LT group (control group) was
enrolled by a surgeon who was not related to this study. Both
groups were compared concerning age (years), sex (male, fe-
male), white blood cell (WBC) count, neutrophil count, lym-
phocyte count, platelets, red cell distribution width (RDW),
platelet distribution width (PDW), mean corpuscular hemo-
globin (MCH), mean platelet volume (MPV), mean corpuscular
volume (MCV), bilirubin level, CRP level, white cell neutrophil
to lymphocyte ratio (NLR), platelets, red cell distribution width (RDW),
white cell lymphocyte ratio (WLR), platelet to lymphocyte ratio (NLR),
platelet to neutrophil ratio (PNR), appendix diameter
(mm), appendix length (mm), presence of acute appendicitis,
ultrasonographic findings, and histopathological findings.

Immunosuppression for LT Recipients

Intravenous methylprednisolone was administered immedi-
ately after the completion of the hepatic artery anastomosis
during liver graft implantation. Thereafter, peroral steroid
treatment was initiated on a postoperative day one and ta-
pered from 100 mg/day to 0.25 mg/kg/day and stopped 3-6
months after surgery, except in patients with autoimmune
diseases. Cyclosporine was the first choice in pediatric pa-
tients who underwent LT due to acute liver failure or neuro-
llogical Wilson’s disease. Mycophenolate mofetil and tacrolim-
us were usually initiated on postoperative day 3. Tacrolimus
was the first choice for immunosuppressive therapy in most
cases except in patients with renal dysfunction or hepatore-
nal syndrome. In patients with impaired or deteriorated renal
function, tacrolimus was stopped or tapered and everolimus
was added until renal function improved.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Sta-
tistics v25.0 (Statistical Package for the Social Sciences, Inc,
Chicago, IL, USA). The quantitative variables were expressed
as, median and min-max. The qualitative variables were re-
ported as number and percentage (%). Kolmogorov-Smirnov
test was used to determine whether the quantitative vari-
ables showed normal distribution. Mann-Whitney-U test was
used to compare the quantitative variables. Fisher’s exact
tests were used to compare qualitative variables because the
minimum expected count was less than 5 for all compared
parameters. A p-value of less than 0.05 was considered sta-
tistically significant. Patient medical records were retrospec-
tively reviewed after obtaining approval from Inonu Univer-
sity institutional review board for non-interventional studies
(Approval No: 2019/16-381).

RESULTS

A total of 65 patients (41 male and 24 female) aged between
one year and 84 years were included in this case-control study.
While the age of the 52 patients (32 male and 20 female) in the
non-transplant group ranged from 17 years to 84 years,
the age of the 13 patients (nine male and four female) in the
LT group ranged from one year to 64 years. Patients in the LT
group underwent appendectomy with a preliminary diagnosis
of AAP a median 339 days (min-max: 20–2023 days) after LT.
While living donor LT was performed in 10 patients in the LT
group, deceased donor LT was performed in the remaining
three patients. Eleven of the patients in the LT group were
adults, and the remaining two were in the pediatric age group
(one and eight years).

There was no statistically significant difference between
the groups concerning age (p=0.163), sex (p=0.753), PDW
(p=0.700), MCH (p=0.115), MPV (p=0.611), MCV (p=0.081),
TBil (p=0.528), NLR (p=0.228), PLR (p=0.682), WLR
(p=0.412), diameter of appendix (p=0.717), presence of acute appendicitis
according to histopathological findings (p=0.477),
ultrasonographic findings (p=0.139), and detailed histopatho-
logical findings (p=0.064). However, statistically significant dif-
ference was noted between the groups with respect to WBC
count (p=0.002), neutrophil count (p=0.002), lymphocyte
count (p=0.032), platelet count (p=0.032), RDW (p=0.001),
CRP level (p=0.009), PNR (p=0.042), WNR (p=0.03), and ap-
pendix length (p<0.001).

The negative appendectomy rate was relatively higher in the
LT group than in the non-LT group, but this difference was
not statistically significant (30.8% vs. 21.2%; p=0.477). Similar-
ly, the clinical and histopathologically-proven perforated AAp rate was higher in the LT group than in the non-LT group; however, this difference also was not statistically significant (30.8% vs. 9.6%; p=0.070). There was no significant difference between the two groups in terms of postoperative wound infection, wound dissociation, intra-abdominal abscess, and adjacent organ injury. In both groups, the subcutaneous collection was treated with simple drainage in only one patient.

**Table 1.** Comparison of the LT and No-LT appendectomy groups in terms of continuous variables

| Patients' characteristics | LT Group (n=13) | No-LT Group (n=52) | p  
|---------------------------|-----------------|-------------------|------
| Age, median (min–max)     | 42 (1–67)       | 30 (17–84)        | 0.163
| WBC, median (min–max)     | 7.5 (2.5–25)    | 12.5 (6.2–27)     | 0.002
| Neutrophil, median (min–max) | 5.2 (2–20.7)  | 10.2 (3.9–22.3)  | 0.002
| Lymphocyte, median (min–max) | 1.3 (0.4–1.9)  | 1.8 (0.2–5.6)     | 0.032
| Platelets, median (min–max) | 147 (76–503)   | 237 (53–443)      | 0.032
| RDW, median (min–max)     | 14.7 (12.8–17.6) | 13.1 (11.5–18)   | 0.001
| PDW, median (min–max)     | 14.8 (9–18.8)   | 14.8 (8.7–17.6)   | 0.700
| MCH, median (min–max)     | 27 (17.9–32.9)  | 29 (19.6–31.5)    | 0.115
| MPV, median (min–max)     | 9.4 (6.8–11.5)  | 9.2 (5.4–11.9)    | 0.611
| MCV, median (min–max)     | 82.5 (62.6–99.5) | 85.4 (68.4–94.2) | 0.081
| TBil, median (min–max)    | 1 (0.2–2.3)     | 0.8 (0.2–3.7)     | 0.528
| CRP, median (min–max)     | 6.1 (0.3–20.7)  | 0.8 (0.1–16.7)    | 0.009
| NLR, median (min–max)     | 5 (2.3–12.4)    | 5.4 (1.4–29.5)    | 0.228
| PLR, median (min–max)     | 169 (49–429)    | 139 (29–1020)     | 0.682
| PNR, median (min–max)     | 32 (14.5–58.1)  | 22.4 (8.5–95.6)   | 0.042
| WLR, median (min–max)     | 6.3 (4–13.9)    | 6.7 (2.8–31)      | 0.412
| WNR, median (min–max)     | 1.4 (1.1–1.7)   | 1.2 (0.7–2.3)     | 0.030
| Appendix length (mm), median (min–max) | 47 (30–80) | 70 (45–110) | <0.001
| Appendix diameter (mm), median (min–max) | 8 (5–40) | 10 (5–30) | 0.717

LT: Liver transplantation; WBC: White blood cell; RDW: Red cell distribution width; PDW: Platelet distribution width; MCH: Mean corpuscular hemoglobin; MPV: Mean platelet volume; MCV: Mean corpuscular volume; CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNR: Platelet to neutrophil ratio; WLR: White cell lymphocyte ratio; WNR: White cell neutrophil ratio; Min: Minimum; Max: Maximum.

**Table 2.** Comparison of the LT and No-LT appendectomy groups concerning categorical variables

| Patients' characteristics | LT Group (n=13) | No-LT Group (n=52) | p  
|---------------------------|-----------------|-------------------|------
| Sex                       | Male            | 9 (69.2)          | 32 (61.5) | 0.753
|                           | Female          | 4 (30.8)          | 20 (38.5) | 0.477
| AAp                       | Yes             | 9 (69.2)          | 41 (78.8) | 0.477
|                           | No              | 4 (30.8)          | 11 (21.2) | 0.070
| Perforation               | Yes             | 4 (30.8)          | 5 (9.6)   | 0.070
|                           | No              | 9 (69.2)          | 47 (90.4) | 0.070
| Ultrasonographic findings | AAp (+)         | 3 (33.3)          | 32 (64.0) | 0.139
|                           | AAp (-)         | 6 (66.7)          | 18 (36.0) | 0.064
| Histopathological findings| AAp             | 5 (38.5)          | 36 (69.2) | 0.064
|                           | AAp (perforated)| 4 (30.8)          | 5 (9.6)   | 0.064
|                           | Appendix vermiformis | 0 (0.0)  | 5 (9.6)   | 0.064
|                           | Fibrous obliteration | 1 (7.0)  | 2 (3.8)   | 0.064
|                           | Lymphoid hyperplasia | 3 (23.1) | 4 (7.7)   | 0.064

AAp: Acute appendicitis; LT: Liver transplantation.
Comparison of the LT and No-LT appendectomy groups in terms of continuous and categorical variables were summarized in Table 1 and Table 2.

DISCUSSION

AAp is the most common disease requiring emergency surgical therapy worldwide and its current global incidence is 100–151 per 100,000 population.[9,10] Conversely, its incidence following solid organ transplantation is low compared to that in the normal population. However, as the frequency of solid organ transplantation is increasing with enhanced survival due to recent advancements in immunosuppressive therapy, the incidence of AAp in this subgroup of patients is increasing.[5,8,9,11] The first publication regarding AAp in patients with LT was published in 2005 by Abt et al.[11] and since then, 14 articles have been published with one being a review article.[2–16]

Our literature review with 33 LT patients who received appendectomy for AAp has been summarized in Table 3. The studies in the field show that AAp incidence in patients with LT ranges between 0.09%–0.67%.[4,6,8,9,11,13] De’Angelis et al.[9] found that AAp developed in 0.29% of the transplant patients and 38.9% of them had undergone an LT. In our opinion, the term incidence used for documenting AAp occurrence following solid organ transplantation is inappropriate, considering its low rate of occurrence. In fact, we believe “prevalence” is a better term to define the frequency of this disease in transplant patients.

It has been suggested by many researchers that the classical signs and symptoms of AAp, such as right lower quadrant pain, loss of appetite, nausea and vomiting, and fever, are not observed in transplant patients due to the suppressive effects of immunosuppressive therapy, which in turn delay the diagnosis and increase the complication rates observed. On the contrary, some researchers state that in this subgroup of patients, the signs and symptoms of the disease are not different; rather, the severity of the symptoms may be altered.[4,6–8] It has been suggested that combined immunosuppressive therapy used, especially in the early post-transplant period, could mask the symptoms of AAp by suppressing the inflammatory response and result in atypical manifestations of the disease.[7] Furthermore, graft-related complications encountered in the early post-transplant period could also mask the clinical manifestations of the AAp.[3]

As a result of the literature analysis we performed, fever-related data of 21 patients were retrieved, and 66.7% of these patients developed a fever during AAp episodes. In our case-control study, we found that 23.7% of the patients with LT had a fever during the development of AAp. In the literature, the interval between LT and development of AAp was reported to be 8–5430 days, and in 24.2% of the patients, AAp developed in the first 15 days following LT. Our case-control study showed that in 7.7% of the patients, AAp developed in the first postoperative month. Thus, based on our results, we disagree with the idea of the other researchers[7] proposing that AAp develops in the early postoperative period in LT patients.

Some researchers have proposed that immunosuppressive therapy reduces the leukocyte count and suppresses the inflammatory response leading to a delayed diagnosis of AAp.[7,8,14] The opponents of this hypothesis state that there is, in fact, no difference concerning leukocyte count between transplanted and non-transplanted patients with AAp. Shepard and colleagues[5] have stated that leukocytosis was observed in 73% of the LT patients with AAp, comparable to that in the non-transplanted patient population, and their hypothesis was supported by Savar et al.[4] Our literature review showed that 28 of the 33 patients reported had data regarding leukocyte count, and 71.4% of these patients had leukocytosis (>10,000 cells/mm³). In our case-control study, leukocytosis was observed in 30% of the LT patients in contrast to 76.9% of the non-transplant patients during the study period. The results of the study by Fonseca-Neto et al.[4] are consistent with the findings obtained in our study. All in all, our results and the results of previous studies regarding this subject are contradictory. However, in our experience of over 2500 cases of LT, leukocyte levels in the post-transplant period are lower than the normal range observed in the general population as a result of immunosuppressive therapy.

The diagnosis of AAp in LT patients requires evaluation of anamnesis, physical examination findings, laboratory values, and imaging studies. The differential diagnosis in LT patients with AAp should include intraabdominal infections, gastrointestinal perforations, biliary fistula, graft-related complications, rejection, and vascular thrombosis.[9,5,13] As previously discussed, the leukocyte count and inflammatory response are reduced in immunosuppressed individuals. On the contrary, some studies state that inflammatory markers, such as RDW and CRP level, are elevated significantly in LT patients in contrast to non-transplant patients. However, when analyzed in detail, these parameters were found to be especially increased in complicated cases.[12] Therefore, although statistically not significant, a higher perforation rate in the LT patients may explain the elevated CRP and RDW levels. Further, even though ultrasonography is a very effective diagnostic tool when performed by experienced personnel, abdominal computerized tomography is both effective in diagnosing complications related to the transplanted graft and also has higher sensitivity (91% vs. 78%) and specificity (90% vs. 83%) when compared to ultrasonography.[8,4] Radiological studies are especially useful in post-transplant patients in whom leukocytosis is not observed.[9,15]

The majority of researchers have found no difference concerning the etiopathogenetic factors of AAp between transplant and non-transplant patients.[8,9,13] However, there are
Table 3. Summary of the published articles on acute appendicitis after liver transplantation in the literature

| References          | Year    | Country | Study Period | Age | Sex | Etiology     | Duration of symptoms | Total LT | Total App | App (%) | From LT to App (days) | WBC | Fever (≥37.5°C) | Tachycardia |
|---------------------|---------|---------|--------------|-----|-----|--------------|----------------------|----------|-----------|---------|----------------------|-----|----------------|------------|
| Huang et al.        | 2017    | China   | NS           | 58  | M   | HCC          | Sudden onset         | NS       | 2         | NS      | 9                   | 11,000 | Yes           | Yes        |
| Sheppard et al.     | 2017    | USA     | 1998-2013    | 56  | F   | HCC          | NS                   | NS       | 1         | 0.23    | 3650                 | 12,500 | No            | Yes        |
| Foncesa-Neto et al. | 2016    | Brazil  | 2002-2014    | 49  | F   | NS           | NS                   | NS       | 5         | 0.54    | 720                  | NS    | NS            | NS         |
|                      |         |         |              | 38  | F   | NS           | NS                   | 570      | NS        | NS      | NS                   | NS    | NS            | NS         |
|                      |         |         |              | 41  | M   | NS           | NS                   | 180      | NS        | NS      | NS                   | NS    | NS            | NS         |
|                      |         |         |              | 58  | M   | NS           | NS                   | 90       | NS        | NS      | NS                   | NS    | NS            | NS         |
| McCarty et al.      | 2015    | USA     | NS           | 50  | M   | Alcoholic    | 21 days              | NS       | 1         | NS      | 180                 | 6,100  | Yes           | Yes        |
| Andrade et al.      | 2014    | Brazil  | 2010-2013    | 43  | M   | PSC          | 7 days               | 150      | 1         | 0.67    | 12                  | 12,060 | No            | No         |
| Wei et al.          | 2014    | Taiwan  | 2003-2013    | 52  | M   | HCV+HCC      | Several hours        | NS       | 1         | NS      | 240                 | 5,456  | No            | No         |
| Quartey et al.      | 2012    | USA     | NS           | 29  | F   | PSC+ALF      | 12 hours             | NS       | 1         | NS      | 720                 | 13,600 | No            | No         |
| Wu et al.           | 2011    | China   | 2000-2007    | 63  | M   | HCC          | 24 hours             | 817      | 4         | 0.49    | 8                   | 17,000 | Yes           | NS         |
|                      |         |         |              | 33  | M   | HBV          | 24 hours             | 9        |           |         | 19,000              | Yes    | NS            | NS         |
|                      |         |         |              | 49  | M   | HBV          | 48 hours             | 11       |           |         | 18,000              | Yes    | NS            | NS         |
|                      |         |         |              | 21  | F   | HHE          | 48 hours             | 13       |           |         | 21,000              | Yes    | NS            | NS         |
| Aktas et al.        | 2011    | Turkey  | NS           | 2   | M   | PFIC-II      | 7 days               | NS       | 1         | NS      | 1560                | 18,400 | Yes           | Yes        |
| Ceulemans et al.    | 2010    | Belgium | NS           | 63  | F   | NASH         | 16 hours             | NS       | 1         | NS      | 15                  | 20,390 | No            | NS         |
| Savar et al.        | 2005    | USA     | 1989-2002    | 52  | F   | NS           | NS                   | 3287     | 7         | 0.21    | 574                 | 14,900 | NS            | NS         |
|                      |         |         |              | 73  | M   | NS           | NS                   | 231      |           |         | 4,600                | NS     | NS            | NS         |
|                      |         |         |              | 55  | F   | NS           | NS                   | 809      |           |         | 11,200               | NS     | NS            | NS         |
|                      |         |         |              | 9   | F   | NS           | NS                   | 1050     |           |         | 5,470                | NS     | NS            | NS         |
|                      |         |         |              | 15  | M   | NS           | NS                   | 1598     |           |         | 6,810                | NS     | NS            | NS         |
|                      |         |         |              | 1   | M   | NS           | NS                   | 2977     |           |         | 18,080               | NS     | NS            | NS         |
|                      |         |         |              | 56  | F   | NS           | NS                   | 2935     |           |         | 10,580               | NS     | NS            | NS         |
| Abt et al.          | 2005    | USA     | 1996-2004    | NS  | NS  | NS           | 14 hours-3 days      | NS       | 8         | 0.09    | 21-5430             | 2.3-26.400 | Yes (n=6)     | NS         |
Table 3. Summary of the published articles on acute appendicitis after liver transplantation in the literature (continued)

| References         | Diagnostic tools | Perforation | Surgery                  | Postoperative complications | Histopathological findings | Hospital stay (day) | Follow up (day) | Immunosupp. regimens | Status    |
|--------------------|------------------|-------------|--------------------------|-----------------------------|----------------------------|---------------------|------------------|----------------------|-----------|
| Huang et al.       | CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | 7                   | 270              | Combined            | Alive     |
| Sheppard et al.    | CT               | Yes         | Appendectomy (Converted) | No                          | NS                         | 7                   | NS               | Combined            | Alive     |
| Fonseca-Neto et al.| CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | 1                   | NS               | Combined            | Alive     |
| NS                 | Yes              | Appendectomy (Open) | Wound infection?             | AAp                         | 45                         | NS                  | NS               | Alive                |
| Sheppard et al.    | CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | 2                   | NS               | NS                   | Alive     |
| NS                 | Yes              | Appendectomy (Open) | Wound infection?             | AAp                         | 30                         | NS                  | NS               | Alive                |
| McCarty et al.     | CT               | No          | Appendectomy (Lap)       | No                          | AAp (CMV+)                 | 6                   | 360              | Combined            | Alive     |
| Andrade et al.     | CT (No-diagnostic)| No         | Appendectomy (Open)      | Sepsis                      | NS                         | 4                   | 4                | Single              | Dead      |
| Wei et al.         | CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | NS                  | NS               | NS                   | Alive     |
| Quartey et al.     | CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | NS                  | 150              | Combined            | Alive     |
| Wu et al.          | Examination      | No          | Appendectomy (Open)      | No                          | AAp                        | NS                  | 2520             | Combined            | Alive     |
| Examination        | No                | Appendectomy (Open) | No                          | AAp                        | NS                         | 1860                | Induced           | Alive                |
| Aktas et al.       | CT               | Yes         | Appendectomy (Open)      | No                          | AAp                        | NS                  | 1200             | Combined            | Alive     |
| Ceulemans et al.   | CT               | No          | Appendectomy (Lap)       | No                          | AAp                        | 12                  | NS               | Combined            | Alive     |
| Savar et al.       | CT               | NS          | Appendectomy (Open; n=7) | No                          | NS                         | NS                  | NS               | NS                   | Alive (n=7) |
| Abt et al.         | US (n=8)         | Yes (n=4)   | Appendectomy (Open)      | Wound infection (n=2)       | AAp (n=8)                 | 3-12 days           | 210-2220         | NS                   | Alive (n=8) |

LT: Liver transplantation; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALF: Acute liver failure; NASH: Nonalcoholic steatohepatitis; PSC: Primary sclerosing cholangitis; HHE: Hepatic hemangioendothelioma; PFIC-II: Progressive familial intrahepatic cholestasis; CMV: Cytomegalovirus; CT: Computed tomography; US: Ultrasonography; AAp: Acute appendicitis; NS: Not-stated; Lap: Laparoscopic.
some opponents of this opinion. In fact, luminal obstruction and bacterial overgrowth are the two triggering factors in the development of clinical AAP. Our literature review revealed that only one LT patient had acute appendicitis due to CMV infection. Further, CMV-associated AAP is more common after kidney and bone marrow transplantation.

The gold standard therapeutic option for AAP is open or laparoscopic appendectomy. The timing of appendectomy depends on the development of complications (pylephlebitis, periappendicular abscess, and plastron) at the time of diagnosis. The basic principles of management for AAP in LT patients are the same as those for non-transplant patients. Our literature review showed that 27 transplanted patients had received open appendectomy, whereas five transplanted patients underwent laparoscopic appendectomy. In the remaining patient, a perforation was noticed during laparoscopic exploration and the operation was converted to open surgery. Although laparoscopic surgery is recommended in the early postoperative period, laparoscopic appendectomy may also be performed many years after the transplant surgery. The first trocar should always be placed under direct vision during laparoscopic appendectomy. In the open approach, if the diagnosis is confirmed in the preoperative period, a McBurney incision is preferred. Conversely, in cases with uncertain diagnoses, the old incision or midline incision should be used for the exploration of the abdomen.

In the present case-control study, 12 LT patients underwent operation through the McBurney incision, and one patient received a paramedian incision for an appendectomy.

The most dreaded complications of appendicitis in transplant patients are perforation and intraabdominal sepsis. The rate for perforation in the non-transplant population ranges between 4–41.5%, whereas it was reported to be 0–50% in LT patients. Abt et al. showed that in LT patients in whom the diagnosis was delayed or the admission was delayed by three days, the perforation rate was 75%. This is supported by many other researchers. Our literature review showed that among the 26 patients with documented operative parameters, the perforation rate was 30.7%, and no mortality case was noted. In previous literature, during the 4–2220 days of follow up, only one case of mortality related to AAP was observed. In the present study, 30.8% of the 13 LT patients developed perforation and none of the patients died. In our opinion, the main causes of perforation were the non-specific symptoms observed in the patients enrolled and late admission to the emergency department. Conversely, a high negative appendectomy rate in our institution may be attributable to our decision to operate in LT patients suspected to have AAP to avoid any complications.

In conclusion, to our knowledge, this study is the first study to compare AAP in LT patients to that in the normal population. WBC and neutrophil counts that are biomarkers of inflammation were lower in LT patients; however, the CRP level and RDW, markers of severe appendicitis, were higher in the LT patients. Although AAP has been known to be more frequent in the early post-transplant period, we showed that it may occur at any time following LT. Further, the rates of perforation and negative appendectomy were higher in LT patients than in the normal population, although this difference was not statistically significant. We believe that our results are relevant as, to our knowledge, this is the first and largest study on this subject concerning design and the number of cases reported. In addition, since AAP after LT is a very rare clinical entity, the multicentric study should be designed to comprehensively evaluate AAP in transplanted patients.

Ethics Committee Approval: Approved by the local ethics committee.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: S.A., A.T.; Design: S.A., K.B.S.; Materials: K.B.S., C.K., A.T.; Data: K.B.S., C.K., A.T.; Analysis: S.A.; Literature search: S.A., C.K., A.T.; Writing: S.A.; Critical revision: S.A., S.Y.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Akbulut S, Koc C, Kocaalan H, Gonuldas F, Samdanci E, Yologlu S, et al. Comparison of clinical and histopathological features of patients who underwent incidental or emergency appendectomy. World J Gastrointest Surg 2019;11:19–26. [CrossRef]
2. Quartey B, Dunne J, Creyer C. Acute appendicitis post liver transplant: a case report and literature review. Exp Clin Transplant 2012;10:183–5. [CrossRef]
3. Aktas S, Sevmys S, Karakayali H, Ozcan F, Coskun M, Bilezikzi B, et al. Acute appendicitis after diaphragmatic hernia after pediatric liver transplant. Exp Clin Transplant 2011;9:63–7. [CrossRef]
4. Savar A, Hiatt JR, Busuttil RW. Acute appendicitis after solid organ transplantation. Clin Transplant 2006;20:78–80. [CrossRef]
5. de’Angelis N, Esposito F, Memmo R, Lizzi V, Martinez-Pérez A, Landi F, et al. Emergency abdominal surgery after solid organ transplantation: a systematic review. World J Emerg Surg 2016;11:43. [CrossRef]
6. Sheppard SE, Marecki HL, Psoinos CM, Movahedi B, Furman MJ, Bzorgezadeh A, et al. Acute Appendicitis after Liver Transplantation: A Case Report and Review of the Literature. Int J Organ Transplant Med 2017;8:208–12. [CrossRef]
7. Huang JF, Ma JF, Gong Y, Yu LL, Cui CX, Yang LX, et al. Acute Appendicitis in the Early Stage after Orthotopic Liver Transplantation. Chin Med J (Engl) 2017;130:1253–4. [CrossRef]
8. Fonseca-Neto OC, Lima HC, Melo PS, Melo PS, Lemos R, Leitao L, et al. Acute appendicitis in liver transplant recipients. Arq Bras Cir Dig 2016;29:30–2. [CrossRef]
9. Andrade RO, Pires RS, Silva RE, Mello FPT, Sousa CCT, Basto ST, et al. Acute Appendicitis after Liver Transplant: A Case Report and Review of the Literature. Open J Organ Transplant Surg 2014;4:29–32. [CrossRef]
10. Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, Chernoff GW, et al. The Global Incidence of Appendicitis: A Systematic Review of Population-based Studies. Ann Surg 2017;266:237–41. [CrossRef]
11. Abt PL, Abdullah I, Korenda K, Frank A, Peterman H, Stephenson GR, et al. Appendicitis among liver transplant recipients. Liver Transpl 2005;11:1282−4. [CrossRef]
12. Ince V, Barut B, Ozdemir F, Ersan V, Kurluturk K, Gonultas F, et al. The management of acute appendicitis in liver transplant patients: How effective is the Alvarado score? North Clin Istanbul 2017;4:262−6. [CrossRef]
13. McCarty TP, Lee RA, Herfel BM, Pappas PG. Cytomegalovirus appendicitis in solid organ transplant patients, two cases and a review. J Clin Virol 2015;66:48−50. [CrossRef]
14. Wei CK, Chang CM, Lee CH, Chen JH, Yin WY. Acute appendicitis in organ transplantation patients: a report of two cases and a literature review. Ann Transplant 2014;19:248−52. [CrossRef]
15. Wu L, Zhang J, Guo Z, Tai Q, He X, Ju W, et al. Diagnosis and treatment of acute appendicitis after orthotopic liver transplant in adults. Exp Clin Transplant 2011;9:113−7. [CrossRef]
16. Ceulemans P, Wybaille E, Monhalii D, Aerts R, Pirenne J. Acute appendicitis after liver transplantation: a case report and review of the literature. Acta Chir Belg 2010;110:335−8. [CrossRef]
17. Akturk OM, Cakir M, Yildirim D, Akinci M. C-reactive protein and red cell distribution width as indicators of complications in patients with acute appendicitis. Arch Clin Exp Med 2019;4:76−80. [CrossRef]
18. Balogun OS, Osinowo A, Afolayan M, Olajide T, Lawal A, Adesanya A. Acute perforated appendicitis in adults: Management and complications in Lagos, Nigeria. Ann Afr Med 2019;18:36−41. [CrossRef]

**ÖRJİNAL ÇALIŞMA - ÖZET**

Akut apandisit ön tanısı ile apendektomi yapılan karaciğer transplantli ve transplant dişi hastaların karşılaştırılması: Olgu kontrol çalışması

**Dr. Kemal Barış Sarıcı, Dr. Sami Akbulut, Dr. Cemalettin Koç, Dr. Adem Tuncer, Dr. Sezai Yılmaz**

İnönü Üniversitesi Tıp Fakültesi, Karaciğer Nakli Enstitüsü ve Genel Cerrahi Anabilim Dalı, Malatya

**AMAC:** Bu çalışmanın amacı akut apandisit ön tanısıyla apendektomi olmuş karaciğer transplantli ve transplant dişi hastaların karşılaştırılmasıdır.

**GEREC VE YÖNTEM:** Posttransplant dönemde akut apandisit ön tanısıyla apendektomi yapılan 13 karaciğer transplantli hasta (transplant grubu) ile aynı dönemde apendektomi olmadan karaciğer transplanti yapılan 52 hasta (non-transplant grubu) demografik ve klinikopatolojik özellikler yönünden karşılaştırıldı. Transplant ve non-transplant gruplar 1:4 rastgele eşleştirme yöntemi kullanılarak oluşturuldu. Devamlı değişkenlerin karşılaştırılmasında Mann-Whitney U-testi kullanılarak kategorik değişkenlerin karşılaştırılmasında Fisher kesin testi kullanıldı. P değeri <0.05 istatistiksel anlamlılık sınırları kabul edildi.

**BULGULAR:** Bu çalışmaya yaşları 1 ile 84 yıl arasında değişen toplam 65 hasta alındı. Non-transplant grubundaki 52 hastanın (32 erkek ve 20 kadın) 17 ile 84 yıl arasında değişiklik transplantoğraf grubundaki 13 hastanın (9 erkek ve 4 kadın) yaşları 1 ile 64 yıl arasında değişiklikti. Gruplar arasında WBC (p=0.002), nötrofil (p=0.002), lenfosit (p=0.032), trombosit (p=0.032), RDW (p=0.001), CRP (p=0.009), PNR (p=0.042), WNR (p=0.03) ve apendiks uzunluğu (p<0.001) açısından istatistiksel olarak anlamli farklılıklar saptandı. Negatif apendektomi oranı transplant grubunda nisbeten daha yüksek olmakla birlikte bu farklılık istatistiksel olarak anlamli değildir (%30.8 ve %21.2; p=0.477). Perfore apandisit transplant grubunda çok daha sık görülebilece birlikte bu farklılık istatistiksel olarak anlamli değildir (%30.8 ve %9.6; p=0.070).

**TARTIŞMA:** WBC ve nötrofil LT grubunda daha duyarlı; CRP ve RDW LT grubunda daha yüksek. Perforasyon ve negatif apendektomi oranları LT grubunda daha yüksek, ancak bu fark istatistiksel olarak anlamli bulunmamıştır.

**Anahtar sözcükler:** Akut apandisit; karaciğer alıcıları; karaciğer nakli; negatif apendektomi; perfor apandisit.

*Ulus Travma Acil Cerrahi Derg 2020;26(5):705-712 doi: 10.14744/tjtes.2020.52368*