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ORIGINAL ARTICLE

Early Detection of Candidaemia Using Mannan Antigen Assay among Liver Transplant Recipients in National Liver Institute, Menoufia University

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ABSTRACT

Background*: Candidia is the most common fungal infection affecting the transplant recipients. Regular monitoring of at-risk patients by detection of circulating Mannan antigen is an aid in early diagnosis of Candidaemia.* ***Objectives****: determination of the hospital risk factors for developing Candidaemia, the average time for occurrence of Candidaemia among living donor liver transplant (LDLT) recipients and evaluation of the value of Mannan antigen in early detection of Candidaemia.* ***Methodology****: This study was conducted on 50 LDLT recipients. All patients were subjected to history taking and complete medical examination. Blood culture was done for detection of Candidaemia and serum Mannan antigen level was measured by EIA technique every five days postoperative for six times.* ***Results:*** *During the first month postoperative 7/50 cases (14%) of our LDLT patients had Candidaemia .The cultures done on the 5th day, were negative for all patients, however serum Mannan antigen was positive in 3 cases (sensitivity 42.9%, specificity 95.3%). In the 10th day only 4 cases were positive by blood culture (sensitivity 57.1%, specificity 100%)., while serum Mannan antigen was detected in the all seven cases (sensitivity 100% specificity 95.3%). On the 15th day, 2 new cases became positive by blood culture (sensitivity 85.7%, specificity 100%), while serum Mannan antigen was still detected in the all 7 cases of Candidaemia (sensitivity 100% specificity 95.3%). Finally on 20rh day postoperative, the last case tested positive by blood culture (sensitivity 71.4%, specificity 85.7%).* ***Conclusion:*** *Serum Mannan antigen is a good tool for early detection of Candidaemia in LDLT recipients.*

INTRODUCTION

Liver transplantation (LT) became the hope of patients with end-stage liver disease, with hepatocellular carcinoma (HCC) and acute liver failure. In Egypt, chronic liver disease is a major health issue and *hepatitis C virus (HCV)* prevalence is 14.7% among the 15−59 years age group. Accordingly, Egypt has the highest HCV prevalence in the world and HCV-associated cirrhosis is the most common indication for orthotopic liver transplantation in Egypt [1].

The first DDLT (dead donor liver transplantation) in the Arab World was performed in 1990, Saudi Arabia [2].

The first LDLT in the Arab world was performed at National Liver Institute in Egypt (1991) and the longest recipient survival was 11 months [3].

Between (1990 and 2013), 3,804 liver transplants were performed at 27 centers in eleven Arab countries. The largest percentage of liver transplantation has been performed in Egypt (9.6% at National Liver Institute) followed by Saudi Arabia and Jordan.[4]

Nowadays, the increased potency of immunosuppressive drugs has improved graft and patient survival after orthotropic liver transplantation (OLT) but has also increased incidence of opportunistic infections (incidence is more than 50% of OLT recipients), which are the leading cause of morbidity and mortality postoperative . Bacterial infections account for most post-transplant infections (up to 70%), followed by viral and fungal infections [5].

The timing of a specific post OLT infection is influenced by the state of immunosuppression, environmental exposure to a specific organism, and development of surgical complications. Infections occur differently in relation to three consecutive time periods following liver transplantation (<1 month, 1-6 months, and >6 months post-OLT) [6]

The incidence of Invasive Fungal Infections (IFIs) after OLT is (5% to 42%) which considered a major cause of postoperative morbidity and mortality.[7]

Candidiasis is the most common fungal infection in the transplant recipient, ranging from mucocutaneous

overgrowth to bloodstream and metastatic infection. It is predominant mainly during immediate postoperative period especially in the first month with a mortality rate 25–69%[8].

These infections have significant impact on patient survival after liver transplantation. So a high degree of suspicion is required for the early diagnosis and accordingly, the optimal management of these infections [9].

The diagnosis of Candidaemia is still difficult due to the lack of specificity of the clinical symptoms and the poor sensitivity of the blood culture. So the combination of serological techniques with direct mycological methods improves the diagnosis in patients at risk [10].

The detection of circulating *Candida* antigens in at risk patients' plasma or serum or is one of the serological approaches available nowadays .Mannan antigen is a polysaccharide non-covalently bound to the yeast cell-wall which appears to be one of the main biomarkers for the diagnosis of Candidaemia[11].

METHODOLOGY

The present study was conducted during the period from January 2015 to July 2017 at National Liver Institute (Egypt). The study protocol was approved by the local ethics committee of Menoufia University. All subjects were be given written informed consent before sharing into the study. It involved 50 LDLT recipients with various clinical diseases who were admitted to Transplantation and I.C.U Departments, National Liver Institute. Patients included in this study were adults and children of both sexes who underwent LDLT with negative blood culture for fungal infection before surgery.

Exclusion criteria:

Any patient taking antifungal treatment before surgery or those with positive blood culture before surgery. All patients were subjected to history taking and complete medical examination. microbiological and serological investigations were done every five days during the first month postoperative for early detection of Candidaemia.

Blood culture:

About 5-10 ml (adult) 2-5ml (pediatric) were withdrawn from LDLT recipients under complete aseptic conditions and inoculated in BacT/ALERT® culture media bottles. Then incubated in BacT/ALERT® system every five days for six times. Subcultures were done on SDA,*Candida* chrome agar and confirmed by VITEK® 2C2 system using yeast identification card [12].

***Candida* score calculation**:

Candida score was used to determine the likelihood of invasive candidiasis vs colonization in critically ill patients using the following parameters: severe sepsis (2 points), total parenteral nutrition (1 point), initial surgery (1 point) and multifocal *Candida* colonization (1 point). Candida score of > 2.5 was classified as a positive (Candida score) so easily identify patients who would benefit from early antifungal treatment [13].

Serum samples:

About 5-7 ml of venous blood was aseptically withdrawn from all subjects. 3 ml was transferred slowly into a plain tube (each patient was tested every five day postoperative and for 6 times). The serum was allowed to separate in a serum separator tube at room temperature then centrifuged at approximately 1000 X g for 15 minutes. The serum samples were stored at -80°C until further use for Mannan antigen assay and repeated freeze-thaw cycles were avoided.[14]

***Mannan* antigen assay:**

Serum Mannan antigen levels were quantified by Platelia® *Candida* Ag plus EIA according to the manufacturer's instructions (Bio-Rad Laboratories, France). Platelia® *Candida* Ag plus EIA is one-stage immunoenzymatic sandwich microplate assay, allowing the detection of the circulating Mannan *Candida* antigen in human serum or plasma using the rat monoclonal antibody (MAb), EBCA-1, which is directed against *Candida* α 1-5 oligomannosides. Positive control, negative control and each sample were treated firstly by adding sample treatment solution then heating in boiling water bath for 3 minutes and finally the supernatant extracted after centrifugation at10.000 g for 10 minutes. The supernatants and the calibrators were added in each well and then the conjugate solution was added to each well, the microplate was incubated for 90 min at 37°C and followed by washing with Working Washing Solution.Chromogen Solution (TMB solution) was added to each well to visualize the enzymatic reaction and then the microplate was incubated in the dark at 25°C for 30 minutes.. TMB was catalyzed to produce a blue color that changed into yellow after adding acidic stop solution. The optical density of each well was read at 450nm, by Multiskan™ FC Microplate Photometer,which is proportional to the Mannan antigen amount of sample captured in plate[15].

RESULTS

Patient characteristics

This study included 50 LDLT recipients with mean age of 35.9±20.2 years old, of them 40 cases were males while 10 were females. 7/50 cases (14 %) of the participants were diagnosed having Candidaemia during the postoperative first month while 43/50 cases (84 %) were negative. The total deaths in the first month after surgery were 14/50 cases (28 %) with 5 cases (35.7%) due to Candidaemia (Table 1)

Table 1: Patient characteristics

Item	Frequency	Percentage
Gender		
Males	40	80%
Females	10	20%
Age(years)		
Mean ± SD	35.9±20.2	
Min- max	1-61	
Diagnosis		
Blood candidiasis	7	14%
No blood candidiasis	43	86%
Survival after surgery		
Died (n=14):		
Candidaemia	5	71.4%
No Candidaemia	2	20.9%
Survived (n=36):		
Candidaemia	**9**	28.9%
No Candidaemia	**34**	79.1%

There was a high–statistically significant difference between the two groups (those with Candidaemia and those without) regarding death rate, ICU stay, *Candida* score and units of blood transfusion as shown in (table 2).

Table 2: Evaluation of hospital risk factors for developing Candidaemia among LDLT recipients:

Items	Invasive candidiasis (NO=7)	No invasive candidiasis (NO=43)	p-value
MELD score			
- Median -range (Min -max)	12 11-19	15 3-26	**P =0.74 (>0.05)**
***Candida* score**			
- Median -range (Min-max)	4 3-5	2 2-3	**P =0.001* (<0.05)**
Hospital stay			
Median -range (Min-max)	25 17-29	20 10-30	**P=0.08 (>0.05)**
ICU stay			
Median -range (Min-max)	10 5-12	5 4-10	**P=0.00** (<0.001)**
Operation time in hours			
Median -range (Min-max)	12 8-13	10 3-15	**P =0.03* (<0.05)**
Blood transfusion in units			
-Median -range (Min -max)	5 1-10	2 1-8	**P =0.029* (<0.05)**

*significance at <0.05

Most cases that developed Candidaemia (58%) were positive for *Candida* blood culture on the10th day postoperative, while the minorities tested were positive on the subsequent days (15th and 25th day) with high death rates (44%) in early Candidaemia (fig 1)

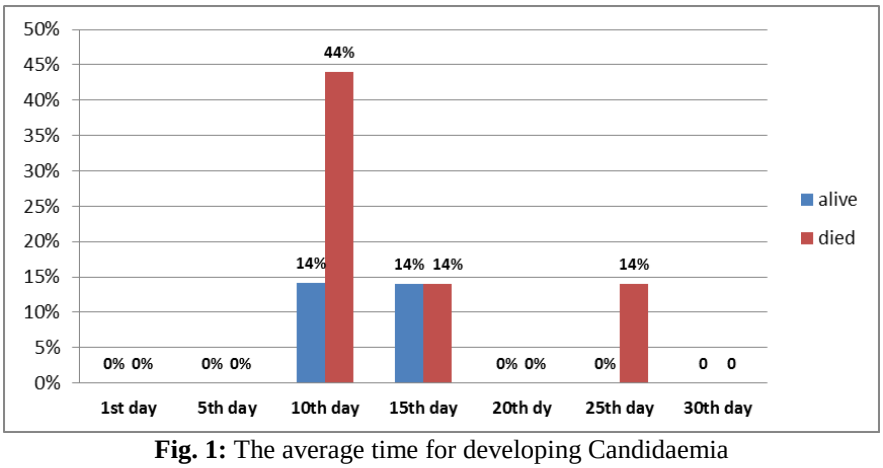

Fig. 1: The average time for developing Candidaemia

All living patients who developed Candidaemia (2/2 cases) had *C.albicans* as the single isolate from blood culture (fig 2). In contrast to the dead cases which had *Candida* non *albicans* with a total percentage of 60% (20% *C.tropicalis*, 20% *C.ceferrii* and 20% *C.glaberta*) (Fig. 3)

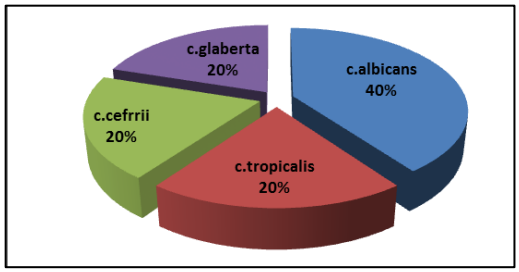

Fig. 2: Distribution of Candida species among died cases of Candidaemia

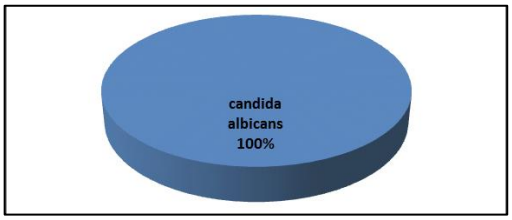

Fig. 3: Distribution of *Candida* species among living cases of Candidaemia

In the 5th day, the blood cultures for all patients were negative; however serum Mannan antigen was positive in 3 cases (sensitivity 42.9%, specificity 95.3%). In 10th day 4 cases were positive by blood culture (sensitivity 57.1% ,specificity 100%), while serum Mannan antigen was detected in the all 7 cases of Candidaemia (sensitivity 100% specificity 95.3%).

In the 15th day 2 new cases became positive by blood culture (sensitivity 85.7%, specificity 100%), while serum Mannan antigen was still detected in the all 7 cases of Candidaemia (sensitivity 100% specificity 95.3%).

Finally in 20th day the last case appeared by blood culture (sensitivity 71.4% specificity 85.7%). We found that the best time for Mannan Ag assay to detect early Candidaemia was postoperative the 10th day (sensitivity100%) while blood culture sensitivity was only (57.1%). (table 3)

Table 3: Sensitivity and specificity of blood culture in comparison to Mannan antigen assay for detection of Candidaemia at 10th day postoperative

Item	Of blood culture	Of serum antigen
Sensitivity	(4/7)*100=57.1%	(4/7)*100=100%
Specificity	(43/43)*100=100%	(41/43)*100=95.3%
Positive predictive value	(4/4) *100=100%	(7/9) *100=77.8%
Negative predictive value	(43/46)*100=93.5%	(41/41)*100=100%

On the 15th day, inspite of the increased sensitivity of blood culture (85.7%), Mannan Ag was still of a high sensitivity (100%), (table 4)

Table 4: Sensitivity and specificity of blood culture in comparison to Mannan antigen assay for detection of Candidaemia at 15th day Postoperative

Item	Of blood culture	Of serum antigen
Sensitivity	(6/7) *100= 85.7%	(7/7) *100= 100%
Specificity	(43/43) *100=100%	(40/43) *100= 93.1%
Positive predictive value	(6/6) *100=100%	(7/10) *100=70%
Negative predictive value	(43/44) *100=97.8%	(40/40) *100=100%

On the 20th day, the sensitivity of blood culture decreased again (71.4%) and the sensitivity of Mannan Ag also decreased but slightly (85.7%) (table 5).

Table 5: Sensitivity and specificity of blood culture in comparison to Mannan antigen assay for detection of Candidaemia at 20th day postoperative

Item	Of blood culture	Of serum antigen
Sensitivity	(5/7) *100= 71.4%	(6/7) *100= 85.7%
Specificity	(42/43) *100= 97.3%	(42/43) *100= 97.7%
Positive predictive value	(5/6) *100= 83.3%	(6/7) *100= 85.7%
Negative predictive value	(42/44) *100= 9.5%	(42/43) *100= 97.7%

Unfourtanatly, the sensitivity of both tests decreased on the subsequent days but Mannan Ag assay was still more sensitive than blood culture (Table 6 and 7).

Table 6: Sensitivity and specificity of blood culture in comparison to Mannan antigen assay for detection of Candidaemia at 25th day postoperative

Item	Of blood culture	Of serum antigen
Sensitivity	(1/3)*100=33.3%	(0/0)*100=0%
Specificity	(35/36)*100=97.2%	(36/36)*100=100%
Positive predictive value	(1/2)*100=50%	(0/0)*100=0%
Negative predictive value	(35/37)*100=94.6%	(36/39)*100=92.3%

Table 7: Sensitivity and specificity of blood culture in comparison to Mannan antigen assay for detection of Candidaemia at 30th day postoperative

Item	Of blood culture	Of serum antigen
Sensitivity	(3/4)*100=75%	(2/4)*100=50%
Specificity	(39/41)*100=95.1%	(40/41)*100=97.6%
Positive predictive value	(1/3)*100=33.3%	(2/6)*100=66.6%
Negative predictive value	(39/42)*100=92.9%	(40/42)*100=95.2%

DISCUSSION

Invasive Fungal Infections (IFIs) are a major cause of morbidity and mortality among OLT recipients with an occurrence rate of (5% to 42%). Candidiasis (60%-80%) and Asperillosis (1%-8%) represent the most common mycoses in these patients, with associated mortality rate of (30% to 50%) and 65% to 90%), respectively [7].

Candida spp. account for 9% of nosocomial blood stream infections (BSIs), making it the fourth most common cause of nosocomial BSIs in the United States .Candidaemia may lead to an increase in the mortality rates up to 35%, with prolongation of hospital stay up to 10 days along which elevated costs [16].

In our study, we found that the incidence of Candidaemia among patients who underwent orthotropic liver transplantation surgeries at the National Liver Institute from(January 2015 to July 2017) was 7/50 patients (14%) and most cases developed Candidaemia (58%) on the 10th postoperative, while the minorities developed it on the subsequent days (15th and 25th day).

This was in agreement with a study done at Wady El-Nile hospital, Egypt(from 2011 to 2013) which reported that the incidence rate of Candidaemia among LDLT recipients was 17/ 140 patients (12.1%) and their infection developed early in the first postoperative 90 days.[8]

In another study which was done from 2003 to 2010 on 22 children at the National Liver Institute, Menofiya University, Egypt [16], the incidence of fungal infection after Living Donor Liver Transplantation was 17.8% peaking at the 2nd week.

Husain, et al. [18] analyzed 35 IFI cases and they found that the median time of infection was 13.5 days, with 72% of infections occurring within the first month after transplantation.

In our opinion, this high rate of fungal infections during the first month post-operatively may be due to the significant suppression of the immunity by the high dose of immunosuppressive therapy taken to avoid early graft rejection.

In addition, Rabkin,et al.[19] reported IFIs in their patients in the first 120 days following liver transplantation with 15 days mean time interval between transplantation and the development of fungal infection.

In a study conducted across 10 centers in Europe (2011–2013) the overall incidence of invasive *Candida* infections (ICIs) was 3.47%, of which, Candidaemia accounted for the majority of cases (57.1%). The median number of days between transplantation and infection onset was 151 days with about (34.1% to 46.3%) of ICIs cases occurred during the first month and within 3 months after surgery, respectively. This indicated that there no significant differences were detected between early and late ICIs regarding clinical presentation.[20]

In our work, a significant association was detected between Candidaemia and the overall 30-day mortality rate among liver transplantation recipients (71.4 % mortality rate in patients with Candidaemia vs. 20.9% in patients without).

These finding were in agreement with Bassetti, et al. [20] who found the overall 30-day mortality due to ICIs was 23.8% with about 34.1% and 46.3% of cases occurring during the first month and within 3 months post operatively. Candidaemia was more common among non survivors (90% vs 46.9%).

In contrast to our results, Mukhtar, et al.[8] found that, the mortality rate was not significantly different between cases with fungal infection and those without (21.7% and 17.9%).

The present study showed that the most common isolated *Candida species* from dead cases were *C. albicans* (40%), followed by *C. tropicalis* (20%) and *C. glaberta* (20%), while *C.albicans* being the single most common isolate from the survivors.

In the TRANSNET (Transplant-Associated Infection Surveillance Network in USA) study (from 2001 to 2006) *Candida albicans* (46.3%) was the most common species, followed by *Candida glabrata* (24.4%) and *Candida parapsilosis* (8.1%). The 90-day mortality was (22.6%) for *C. albicans*, (27.7%) for *C. glabrata*, (31.5%) for *Candida krusei*, (35.2%) for *C.parapsilosis*, and the highest was for *Candida tropicalis* (44%). [21]

Regarding the factors related to acquiring Candidaemia in LDLT recipients, we noticed that high *Candida* score (P value 0.0001), prolonged intensive care unit stay (P value 0.001), long operation time (P value 0.011) and massive blood transfusion (P value 0.029) have a significant association with having Candidaemia, however, there was no statistically significant association between Candidaemia and specific age, sex, prolonged hospital stay , MELD score and ascites degree .

This was also observed by Mukhtar, et al.[8]who also found that most cases of candidemia in LDLT recipients occurring during long ICU stay(1/3 to 1/2 of cases) .

Bassetti, et al.[20] also reported that patients who died were more frequently admitted to ICU compared with the survivors (P value 0.004). but in contrast to our study they found that a MELD score greater than 25 was more frequent among patients who died (P value 0.02).

To investigate the relationship between Candidaemia and early appearance of Mannan Ag in the blood, we regularly tested the level of Mannan Ag in the sera of the study group (every 5 day postoperative till 1 month) with simultaneous blood culture on BacT/ALERT® system. We found that the best time for Mannan Ag assay for early detection of Candidaemia was the 10th day postoperative (sensitivity100%), while blood culture sensitivity was only (57.1%). On the 15th day, the sensitivity of blood culture became better (85.7%), while the sensitivity of Mannan Ag is still (100%).On the 20th day, the sensitivity of blood culture decreased again (71.4%) and the sensitivity of Mannan Ag also decreased but slightly (85.7%).Unfortunately, the sensitivity of both tests decreased on the subsequent days but Mannan Ag assay was still more sensitive than blood culture.

The decline of Mannan Ag level in our opinion may be attributed to two reasons, firstly the immune system against Candidaemia responds by secretion of Mannan antibodies which form an immune complex with Mannan antigen leading to its elimination by the complement system. The second explanation could be the disruption of Mannan antigen molecule by Echinocandin (either Anidulafungin or Micafungin) which was given to the study group as a routine antifungal a postoperative prophylaxis.

Poissy, et al.[22] also compared the sensitivities of Mannan antigen assay to those of the blood cultures and they found that Mannan antigen assay gave the higher positive likelihood ratio than Beta D Glucan (BDG) assay during the crucial period from day 7 before to day 7 after the first positive blood culture (7.7 vs. 1.4 for BDG) .

Duettmann ,et al.[23] evaluated Mannan antibody and antigen as screening in patients with hematological malignancies and bone marrow transplantation and they found that Mannan Ag was highly specific (Specificity 98% & sensitivity 94%) , yet, Mannan antibody failed to detect the only case of invasive *Candida* infection that occurred during the study period .Finally the combination of Mannan Ab and Ag test was inferior when compared with the performance of Mannan Ag alone.

CONCLUSION

Our study highlights the high mortality rates among liver transplant patients associated with *Candida* infections, especially Candidaemia. In this setting, the choice of an adequate therapy is paramount, and risk factors for Candidaemia should be taken into consideration to optimize patients'management.

Colonization by *Candida* species is an important cause of Candidaemia in immunocompromised patients and it depends on duration of hospitalization especialy ICU stay, prolonged operation time and massive blood transfusion.

Detection of early Candidaemia is the goal for appropriate management and this could be achieved by routinely screening LDLT recipient by the serological marker, Mannan Ag assay, instead of waiting for blood culture result which is less sensitive and time consuming.

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