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Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study

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Title: Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study

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Running head: donor bacterial infection on DDLT

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Abstract

Objective: The shortage of available donor organs is an unsolvable concern leading to an expansion in the donor criteria for organ transplantation. Here, we describe our experience and assess the outcomes in recipients who obtained a graft from a donor with bacterial infections in deceased donor liver transplantation (DDLT).

Methods: All DDLTs between January 1991 and February 2017 were retrospectively reviewed. Patients were categorized into two groups based on recipients who obtained a graft from a donor with (Group I) or without (Group II) evidence of bacterial infections. Outcomes and bacterial infections were compared between the two groups of recipients.

Results: Overall, a total of 285 DDLTs were performed from 248 donors consisting of 48 split liver grafts and 208 whole liver grafts. Of those, 98 recipients (Group I, 34.3%) were transplanted with a graft from 78 donors with positive bacterial cultures. Donor sputum cultures had the highest rate of positive bacterial growth, accounting for 26.6% of donors. Overall survival was not significantly different between the two groups (p=0.9746). The overall survival rates at one and three years were 73.5% and 69.2% in the Group I recipients *versus* 68.8% and 62.4% in the Group II recipients. Importantly, no hospital mortality was related to donor-derived bacterial infections.

Conclusion: Transmission of bacteria from the donor to the recipient is infrequent in DDLT. Therefore, potential donors with positive bacterial infections should not be excluded for organ transplantation in order to increase organ availability and ameliorate the organ shortage.

Keywords: deceased donor; bacterial infection; transmission; liver transplantation; outcomes

Strengths and limitations of this study

1. The shortage of deceased organ donors is stringent in Oriental Countries as compared with Western Countries, and thus every donor should be carefully judged for organ transplantation in order to achieve greatest effectiveness.

2. This study enrolled 285 deceased donor liver transplantation in the setting of scarce organ donation, and analyzed the influence of donors with evidence of bacterial infections on liver transplantation.

3. The results show that the incidence of donor-transmitted bacterial infections was very low, suggesting that donors with a bacterial infection should not be excluded as

organ donors for liver transplantation.

4. The study is limited by its retrospective entity in a single transplantation center with a small number of patients.

Introduction

Organ transplantation is a promising alternative for the treatment of many end-stage diseases. However, the discrepancy between organ demand and donor availability is currently an unsolvable concern. Therefore, expanded donor criteria including older donors, circulatory death donors, or donors with mild diseases and so forth are increasingly used as donors for organ transplantation. Subsequently, there is a high possibility of the transmission of unwanted infectious diseases following organ donation. Infectious microbes including viruses, bacteria, parasites and fungi that are present in organ donors have the potential to be transmitted to the transplant recipient.(1-3)

Among these infectious microbes, any active bacterial infection in the donor may result in a lethal complication immediately after transplantation if bacteria are transmitted to the recipient during organ transplantation. Thus, the majority of transplantation surgeons are reluctant to transplant organs known to be infected by active bacteria. Specifically, the deceased donor shortage is very high particularly in Oriental countries. In this study, we gathered our experience in deceased donor liver transplantation (DDLT) and analyzed data regarding donors with bacterial infections to assess the influence of an infected donor on the outcome of the recipient. These

results provide additional information for the selection of deceased donors for liver transplantation (LT).

Methods

Patients

A total of 285 consecutive DDLTs were performed during the period between January 1991 and February 2017 at the Transplantation Institute. All medical records of donors and recipients were retrospectively reviewed under the approval from the Institutional Review Board of Chang Gung Memorial Hospital. Of all LT, liver grafts were procured from 248 donors including 81 donors from the national organ sharing program and 167 donations from the institute. No executed prisoner organs were used in this study. Liver graft donations and transplantations are illustrated in Figure 1. Overall, 40 donors underwent split liver donation, and whole liver grafts were procured from the 208 donors. Among whole liver donors, 13 donors had reduced size liver grafts from a partial liver resected *ex vivo* in order to be implanted in recipients with a relatively small abdominal cavity. Written informed consent was obtained from all patients included.

Donor survey

All potential donors were thoroughly checked by laboratory tests for hepatitis B and C virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), toxoplasmosis and syphilis. Generally, chest radiography and ultrasonography of the heart, liver and kidney would be routinely performed prior to the donation of solid organs. With regard to the assessment of bacterial infection, serial samples including bronchial aspirates, urine and blood were usually obtained for culture. If the donor was eligible for organ donation, transplantation surgeons would proceed to organ procurement after the determination of brain death by specialists.

The decision to perform split liver grafts in two adult recipients was based on preoperative hepatic sonography and an intraoperative assessment of the liver graft. Transection of the hepatic parenchyma for split liver grafts was all performed *in situ* as previously described.(4) Importantly, bile was routinely obtained through the common bile duct for bacterial culture before flushing the biliary tree during liver graft procurement from all donors.

Liver transplantation recipients

All graft implantations were performed using standard techniques without

venovenous bypass. Generally, prophylactic antibiotics were usually administered for all recipients after transplantation unless the susceptibility profile required specific antibiotics prior to transplantation. The selection of prophylactic antibiotics was based on the illness of recipients, in which third-generation cephalosporins was given to recipients with Model For End-Stage Liver Disease (MELD) scores less than 20; a combination of vancomycin and imipenem/cilastatin was administered to recipients with MELD scores above 20. The use of antifungal prophylaxis was optional for recipients who had high risk of fungal infections such as longer hospitalization before transplantation, longer operation time, massive blood loss and blood transfusion during the operation. The immunosuppressive regimen for recipients after transplantation mainly consisted of a combination of methylprednisolone, tacrolimus and mycophenolate mofetil, adjusted based on the clinical assessment of the recipient.

Outcomes and statistical analysis

Recipients were categorized into two groups: Group I consisted of recipients transplanted with a graft procured from a donor with a positive bacterial culture, and Group II included recipients who obtained a graft from a donor without evidence of bacterial infection. Bacterial infection was intensively monitored using samples from the blood, drainage tubes and catheters for all recipients after LT. Microorganisms

than grew in all cultures within 30 days after LT were recorded and assessed for bacterial infection transmission from donor. The recipient's outcome measure was overall survival (OS), which was calculated from the date of LT to the date of death or the end of this study. Survival curves were constructed by the Kaplan-Meier method, and further compared by the log rank test. All data were analyzed using the statistical software SPSS version 20.0 (IBM Inc., Armonk, NY, USA) for Windows. A *p*-value of < 0.05 was defined as statistically significant.

Patient and public involvement statement

This study was a retrospective observational study. Patients were not involved in this study.

Results

Donor features

All donors underwent donation after brain death; the 248 donors consisted of 174 males and 74 females. The median age of the donors was 40 years old, and ranged from 9 to 75 years old. The major causes of brain death were cerebrovascular accidents in 137 donors (55.2%) and head injury in 48 donors (19.4%). The median

duration of stay in the intensive care unit before donation was 3 days (ranging from 1 to 95 days).

Overall, 78 donors (31.5%) had positive bacterial culture samples, in which 3 (1.2%) of them were with triple site positives, 13 (5.2%) were double site positives, and 62 (25%) were only single site positive (Fig. 2). Most positive bacterial cultures were from bronchial aspirates of sputum, which were noted in 66 donors that accounted for 26.6% of all donors and 84.6% of donors with positive bacterial infections. Additionally, bacterial growth was detected in 13 donors (5.2%) from blood cultures, 16 donors (6.5%) from urine cultures, and 7 donors (2.8%) from bile cultures.

Microorganisms in donor cultures

All positive bacterial cultures derived from donors are described in Table 1. A total of 21 bacterial species were identified, including 9 Gram-positive, 11 Gram-negative, and 1 Gram-variable. Among these, the three most common bacteria were *Klebsiella pneumoniae* (*n*=34), *Staphylococcus aureus* (*n*=32), and *Escherichia coli* (*n*=13). *Coagulase-negative Staphylococcus* was the first ranked bacterium found in the blood cultures of 7 donors, and *Escherichia coli* was the most common bacterium found in the urine cultures of 8 donors. *Klebsiella pneumoniae* was isolated from 32 donor sputum cultures and 2 donor bile cultures. Additionally, *Pseudomonas aeruginosa*, a

relative common nosocomial species, was cultivated from 10 donor sputum cultures.

Recipient outcomes

Among the 285 DDLTs, 98 recipients (Group I) obtained grafts from 78 donors with positive bacterial cultures, while the remaining 187 recipients (Group II) were transplanted with grafts from 170 donors who had no evidence of bacterial infection. The clinical characteristics of recipients are summarized and compared in Table 2. The majority of clinical features were similar between the two groups. However, the mean recipient age in Group I was significantly greater than that of Group II recipients ($p = 0.002$), and a significantly higher ratio of Group II recipients received whole liver grafts for transplantation ($p = 0.0002$). Importantly, the rates of bacterial growth from blood cultures and hospital mortality within 30 days after LT were not significantly different between the two groups.

In Group I, only one recipient (1.02%) had *Acinetobacter baumannii* detected in a blood culture after LT, which was the same bacterium cultured from the donor's sputum prior to organ donation. The recipient was indicated for LT due to hepatitis B virus-related end stage liver cirrhosis, and obtained a right liver graft from a split liver donation. However, no evidence of *Acinetobacter baumannii* growth was noted in the blood culture in the other recipient who received a left liver graft from the same donor.

The groups of patients who obtained grafts from donor with and without bacterial infection were compared and similar outcomes were found between the two groups (Fig. 3, $p = 0.9746$). The analysis of the survival curves showed that the overall survival rates at one and three years were 73.5% and 69.2% in Group I recipients, while the corresponding values were 68.8% and 62.4% in Group II recipients.

Discussion

Although LT is currently considered the definitive treatment for individuals with end-stage liver disease, unexpected transmission of infections from the donor to the recipient remains a major concern. Although rare, complication related to donor-derived infectious disease are associated with significant morbidity and mortality. (3, 5-7) Among the types of donor-derived infections, bacterial transmission from the donor could result in bacteremia immediately after transplantation and lead to lethal complications. However, deceased donors are extremely rare in Oriental countries, and the organ shortage for LT is exceptionally large as compared with Western countries.(8, 9) Therefore, every donor should be carefully judged for organ transplantation. This study analyzed donors in terms of bacterial infections in the setting of scarce organ donation. The results show that the incidence of

donor-transmitted bacterial infections was very low, suggesting that donors with a bacterial infection should not be excluded as organ donors for LT.

Generally, bacteria are the most common cause of infections in LT recipients. However, opportunistic infections are generally uncommon in the first 1-4 weeks after transplantation, depending on the recipient's net state of immunosuppression. Thus, unexplained early infections in this period are generally associated with surgery-related complications or donor-derived infections. This study examined all recipient blood cultures for bacteria within 30 days after LT to match the donor's bacterial infection. In line with previous reports, the incidence of possible bacterial transmission from the donor was very low.(10, 11) Only one recipient's blood culture had the same bacterium as the donor, and accounted for only 1.02% of all recipients in the current study.

Acinetobacter baumannii is a typical Gram-negative bacterium that can be an opportunistic pathogen affecting patients with compromised immune systems.(12, 13) However, the recipient who obtained the left liver graft from the same donor had no evidence of this bacterium in their blood cultures after LT. Therefore, the recipient's pathogen could be a hospital-derived nosocomial infection instead of transmission from donor. Meanwhile, liver grafts are usually flushed with organ preserving

solution during organ procurement, and re-perfused with more than 1500 ml/min of the recipient's blood after graft implantation. As such, bacteria within the liver graft are likely to be diluted by these process, and the chance of donor-derived bacterial infection in the recipient is very low.

Our data are similar to previous reports showing that the highest positive rate of bacterial culture of the donor was from sputum cultures.(11, 14) The most common pathogens cultivated from bronchial aspirates of the donors in this study were *Klebsiella pneumoniae* and *Staphylococcus aureus*. Both pathogens are members of the normal flora of the body, and are frequently found in the respiratory tract and skin.(15, 16) *Klebsiella* infections are mostly seen in people with a weakened immune system or a nosocomial infection, and *Staphylococcus aureus* is not always pathogenic. Additionally, *Escherichia coli* was the most common pathogen found in the urine cultures of our donor, which might be related to either translocation from the gastrointestinal tract or contamination with feces. Therefore, culture results from donors that show these pathogens could be ignored so the donors are not excluded from organ donation.

Importantly, each potential donor should be comprehensively screened for medical conditions that may affect the recipient, which might include the presence of

transmissible disease, malignancies, or any other known condition that may be transmitted by the donor organ. However, it is currently impossible to screen potential donors for all potential pathogens during the narrow timeframe of the organ donation process. Specifically, bacterial cultures of potential donors take time and may not provide results prior to organ procurement for transplantation. Likewise, a donor may have a bacterial infection that has been appropriately treated. Under such circumstances, treatment of the recipient for the recognized infection immediately after transplantation might be satisfactory.

Conclusions

Although the study is limited by its retrospective entity in a single transplantation center with a small number of patients, several marked observation might be helpful in clinical practice. Additionally, available organ donor numbers lag behind current and future needs, and this organ shortage has thus forced clinicians to expand the donor pool by using donors with the risk of transmitting infectious diseases. The annual deceased organ donation rate has recently increased to 12.3 per million population in Taiwan, but the number of DDLTs is still not satisfactory, with an average of 100 cases per year.(17) Many other counties may also encounter this situation regarding deceased donor organ transplantation and LT. As a result, a

bacterial infection in the donor should not preclude the use of organs for transplantation. Moreover, the possibility of bacterial transmission from the donor seems to extremely low considering fluid dilution and the non-specific culture results.

Author contributions:
Study concept, design and drafting the manuscript: Kun-Ming Chan
Acquisition of data: Kun-Ming Chan, Tsung-Han Wu, Chih-Hsien Cheng, Chen-Fang Lee, Ting-Jung Wu, Hong-Shiue Chou, Wei-Chen Lee
Critical revision of the manuscript for important intellectual content: Kun-Ming Chan, Wei-Chen Lee

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Patient consents: Obtained.

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Data sharing statement: No additional data available.

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Table 1. Microorganisms cultured from donors.

Micro-organisms	Bacterial cultures				Total
	Sputum	Urine	Blood	Bile	
Gram-positive bacteria					
Staph.aureus	31	–	1	–	32
coagulase-negative staphylococcus	–	–	7	1	8
Enterococcus faecalis	–	5	1	–	6
staphylococcus	1	–	2	–	3
Streptococcus pneumoniae	3	–	–	–	3
Staph.epidermidis	–	1	1	–	2
Aerococcus	–	–	–	1	1
Enterococcus faecium	–	–	–	1	1
Propionibacterium acnes	–	–	–	1	1
Gram-negative bacteria					
Klebsiella pneumoniae	32	–	–	2	34
Escherichia coli	4	8	–	1	13
Pseudomonas aeruginosa	10	2	–	–	12
Haemophilus influenzae	8	–	–	–	8
Enterobacter cloacae	4	3	–	–	7
Acinetobacter baumannii	5	–	1	–	6
Stenotrophomonas maltophilia	2	2	1	1	6
Enterobacter aerogenes	4	–	1	–	5
Veillonella sp	–	–	2	–	2
Proteus mirabilis	2	–	–	–	2
Serratia marcescens	2	–	–	–	2
other					
Gardnerella vaginalis	–	1	–	–	1

Number represent number of patients

Table 2. Recipient characteristics related to donor with or without positive bacterial culture status.

Characteristics	Donor with positive bacterial cultures		*p* value
	Group I: Yes, *n*=98	Group II: No, *n*=187	
Age, median (range)	52 (33–65)	48 (1–67)	0.002
Sex (Male:Female)	77:21	132:55	0.160
Hepatitis status			0.403
Hepatitis B positive	51 (52.0%)	110 (58.8%)	
Hepatitis C positive	21 (21.4%)	27 (14.5%)	
Hepatitis B, C positive	3 (3.1%)	9 (4.8%)	
None	23 (23.5%)	41 (21.9%)	
Indication of LT			0.147
Alcoholic Liver cirrhosis	16 (16.3%)	10 (5.4%)	
Virus-related liver cirrhosis	40 (40.8%)	98 (52.4%)	
Hepatocellular carcinoma	32 (32.7%)	46 (24.6%)	
Others	10 (10.2%)	33 (17.6%)	
MELD score, median (range)	21 (7–40)	23 (7–40)	0.673
Type of grafts			0.0002
Whole liver graft	53 (54.1%)	142 (75.9%)	
Partial liver graft*	45 (45.9%)	45 (24.1%)	
Blood culture after LT (30days)			0.173
Positive bacterial growth	11 (11.2%)	12 (6.4%)	
Negative bacterial growth	87 (88.8%)	175 (93.6%)	
Hospital Mortality (30days)	11 (11.2%)	23 (12.3%)	0.849

LT, liver transplantation; MELD, Model for End-stage Liver Disease. *partial liver grafts included split liver and reduced size liver grafts.

Figure legend

Figure 1. Flow diagram of organ donors and liver transplantations assessed in this study.

Figure 2. The rate of positive bacterial cultures in donors.

Figure 3. Comparison of cumulative overall survival for the patients showing no significant difference between the two groups. Group I (⋯), Group II (—).

Figure 1.

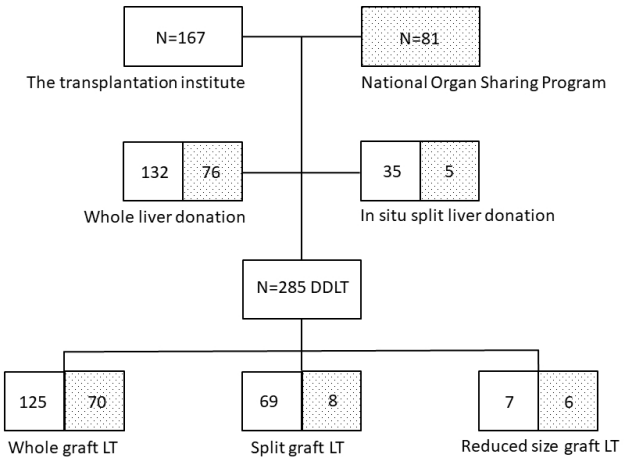

Figure 1

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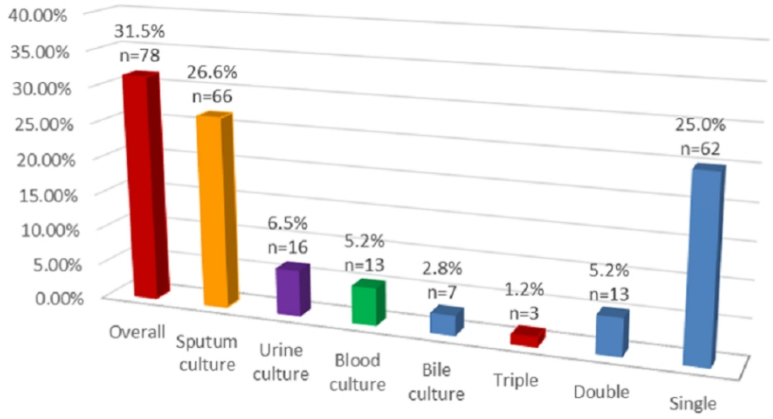

Figure 2.

254x138mm (120 x 120 DPI)

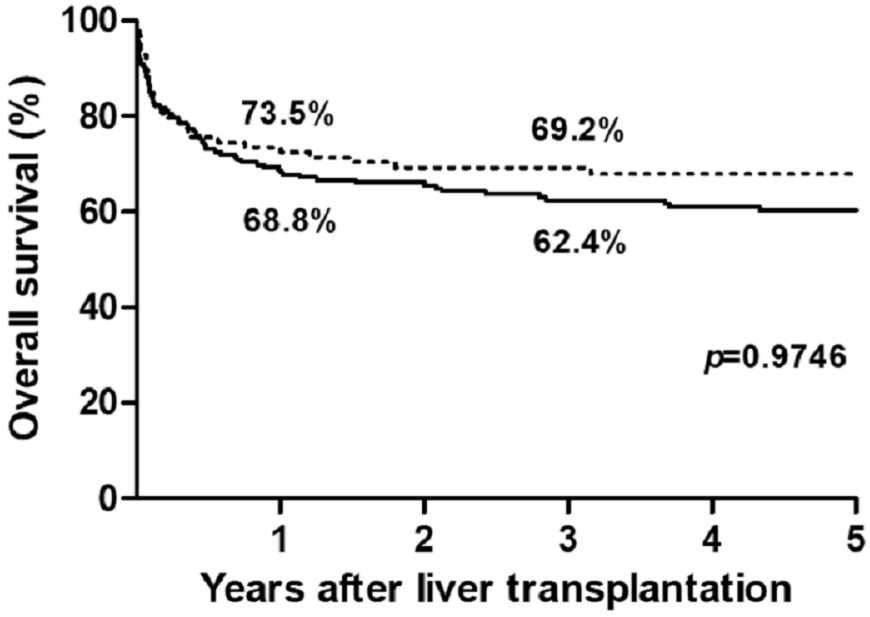

Figure 3.

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5,6
Study design	#4	Present key elements of study design early in the paper	5,6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6,7

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	8,9
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8,9
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8,9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8,9
	#12b	Describe any methods used to examine subgroups and interactions	8,9
	#12c	Explain how missing data were addressed	See note 1
	#12d	If applicable, explain how loss to follow-up was addressed	See note 2
	#12e	Describe any sensitivity analyses	See note 3
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	See note

			4
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9-11
	#14b	Indicate number of participants with missing data for each variable of interest	See note 5
	#14c	Summarise follow-up time (eg, average and total amount)	11
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See note 6
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	16

the present article is based

Author notes

1. n/a, no missing data
2. n/a, no loss follow-up patient
3. n/a, not applicable
4. 6, figure 1
5. n/a, no missing data
6. n/a, not applicable

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Running head: donor bacterial infection on DDLT

Words count: 2146 words; 2 tables, 3 figures

Abstract

Objective: The shortage of available donor organs is an unsolvable concern leading to an expansion in the donor criteria for organ transplantation. Here, we describe our experience and assess the outcomes in recipients who obtained a graft from a donor with bacterial infections in deceased donor liver transplantation (DDLT).

Methods: All DDLTs between January 1991 and February 2017 were retrospectively reviewed. Patients were categorized into two groups based on recipients who obtained a graft from a donor with (Group I) or without (Group II) evidence of bacterial infections. Outcomes and bacterial infections were compared between the two groups of recipients.

Results: Overall, a total of 285 DDLTs were performed from 248 donors consisting of 48 split liver grafts and 208 whole liver grafts. Of those, 98 recipients (Group I, 34.3%) were transplanted with a graft from 78 donors with positive bacterial cultures. Donor sputum cultures had the highest rate of positive bacterial growth, accounting for 26.6% of donors. Overall survival was not significantly different between the two groups (p=0.9746). The overall survival rates at one and three years were 73.5% and 69.2% in the Group I recipients *versus* 68.8% and 62.4% in the Group II recipients. Importantly, no hospital mortality was related to donor-derived bacterial infections.

Conclusion: Transmission of bacteria from the donor to the recipient is infrequent in DDLT. Therefore, potential donors with positive bacterial infections should not be excluded for organ transplantation in order to increase organ availability and ameliorate the organ shortage.

Keywords: deceased donor; bacterial infection; transmission; liver transplantation; outcomes

Strengths and limitations of this study

1. The shortage of deceased organ donors is stringent in Oriental Countries as compared with Western Countries, and thus every donor should be carefully judged for organ transplantation in order to achieve greatest effectiveness.

2. This study enrolled 285 deceased donor liver transplantation in the setting of scarce organ donation, and analyzed the influence of donors with evidence of bacterial infections on liver transplantation.

3. The results show that the incidence of donor-transmitted bacterial infections was very low, suggesting that donors with a bacterial infection should not be excluded as

organ donors for liver transplantation.

4. The study is limited by its retrospective entity in a single transplantation center with a small number of patients.

Introduction

Organ transplantation is a promising alternative for the treatment of many end-stage diseases. However, the discrepancy between organ demand and donor availability is currently an unsolvable concern. Therefore, expanded donor criteria including older donors, circulatory death donors, or donors with mild diseases and so forth are increasingly used as donors for organ transplantation. Subsequently, there is a high possibility of the transmission of unwanted infectious diseases following organ donation. Infectious microbes including viruses, bacteria, parasites and fungi that are present in organ donors have the potential to be transmitted to the transplant recipient.(1-3) The influence of these donor-transmitted infectious diseases on the outcome of organs transplantation could be immediately after transplantation or lasting several years afterward. However, the study focus on assessing donor with bacterial infection and related impact immediately after liver transplantation.

Any active bacterial infection in the donor may result in a lethal complication immediately after transplantation if bacteria are transmitted to the recipient during organ transplantation. Thus, the majority of transplantation surgeons are reluctant to transplant organs known to be infected by active bacteria. Specifically, the shortage of deceased donor is very stringent particularly in Oriental countries. In this study,

donors with bacterial infections were analyzed to assess the influence of an infected donor on the outcome of deceased donor liver transplantation (DDLT). These results provide additional information for the selection of deceased donors for liver transplantation (LT).

Methods

Patients

A total of 285 consecutive DDLTs were performed during the period between January 1991 and February 2017 at the Transplantation Institute. All medical records of donors and recipients were retrospectively reviewed under the approval from the Institutional Review Board of Chang Gung Memorial Hospital. Of all LT, liver grafts were procured from 248 donors including 81 donors from the national organ sharing program and 167 donations from the institute. No executed prisoner organs were used in this study. Liver graft donations and transplantations are illustrated in Figure 1. Overall, 40 donors underwent split liver donation, and whole liver grafts were procured from the 208 donors. Among whole liver donors, 13 donors had reduced size liver grafts from a partial liver resected *ex vivo* in order to be implanted in recipients with a relatively small abdominal cavity. Written informed consent was obtained from

all patients included.

Donor survey

All potential donors were thoroughly checked by laboratory tests for hepatitis B and C virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), toxoplasmosis and syphilis. Generally, chest radiography and ultrasonography of the heart, liver and kidney would be routinely performed prior to the donation of solid organs. With regard to the assessment of bacterial infection, serial samples including bronchial aspirates, urine and blood were obtained for culture before organs donation.

Generally, the potential donor should be hemodynamic stable with acceptable cardiopulmonary function, absence of sepsis or uncontrollable bacterial infection and without malignant neoplasm contraindicated for donation. Donor with virus including hepatitis B, C virus, and HIV (after November 2016) were not contraindicated for organs donation, but could be transplanted to recipient with same viral status. For liver donation, the liver functional reserve of donor should be acceptable and less than 50% of hepatic parenchyma with steatosis. If the donor was eligible for organ donation, transplantation surgeons would proceed to organ procurement after the determination of brain death by specialists. There is no organs obtained from

non-heart beating donor in this study.

The decision to perform split liver grafts in two adult recipients was based on preoperative hepatic sonography and an intraoperative assessment of the liver graft. Transection of the hepatic parenchyma for split liver grafts was all performed *in situ* as previously described.(4) Importantly, bile was routinely obtained through the common bile duct for bacterial culture before flushing the biliary tree during liver graft procurement from all donors.

Liver transplantation recipients

All graft implantations were performed using standard techniques without venovenous bypass. Generally, prophylactic antibiotics were usually administered for all recipients after transplantation unless the susceptibility profile required specific antibiotics prior to transplantation. The selection of prophylactic antibiotics was based on the illness of recipients, in which third-generation cephalosporins was given to recipients with Model For End-Stage Liver Disease (MELD) scores less than 20; a combination of vancomycin and imipenem/cilastatin was administered to recipients with MELD scores above 20. Additionally, antibiotic treatment specific to the recognized microorganisms from donor were also administered after transplantation based on the result of donor's bacterial culture. The use of antifungal prophylaxis was

optional for recipients who had high risk of fungal infections such as longer hospitalization before transplantation, longer operation time, massive blood loss and blood transfusion during the operation. The immunosuppressive regimen for recipients after transplantation mainly consisted of a combination of methylprednisolone, tacrolimus and mycophenolate mofetil, adjusted based on the clinical assessment of the recipient.

Outcomes and statistical analysis

Recipients were categorized into two groups: Group I consisted of recipients transplanted with a graft procured from a donor with a positive bacterial culture, and Group II included recipients who obtained a graft from a donor without evidence of bacterial infection. Bacterial infection was intensively monitored using samples from the blood, drainage tubes and catheters for all recipients after LT. Microorganisms that grew in all cultures within 30 days after LT were recorded and assessed for bacterial infection transmission from donor. The recipient's outcome measure was overall survival (OS), which was calculated from the date of LT to the date of death or the end of this study. Survival curves were constructed by the Kaplan-Meier method, and further compared by the log rank test. Comparison of continuous variables were performed by Student's t test, and categorical variables were compared by the

chi-square or Fisher's exact test as appropriate. All data were analyzed using the statistical software SPSS version 20.0 (IBM Inc., Armonk, NY, USA) for Windows. A *p*-value of < 0.05 was defined as statistically significant.

Patient and public involvement statement

This study analyzed a retrospective data review. There was no patient or public involvement in this study including in the design, recruitment, and conduct of the study.

Results

Donor features

All donors were donation after brain death; the 248 donors consisted of 174 males and 74 females. The median age of the donors was 40 years old, and ranged from 9 to 75 years old. The major causes of brain death were cerebrovascular accidents in 137 donors (55.2%) and head injury in 48 donors (19.4%). The median duration of stay in the intensive care unit before donation was 3 days (ranging from 1 to 95 days). Overall, 78 donors (31.5%) had positive bacterial culture samples, in which 3 (1.2%) of them were with triple site positives, 13 (5.2%) were double site positives, and 62

(25%) were only single site positive (Fig. 2). Most positive bacterial cultures were from bronchial aspirates of sputum, which were noted in 66 donors that accounted for 26.6% of all donors and 84.6% of donors with positive bacterial infections. Additionally, bacterial growth was detected in 13 donors (5.2%) from blood cultures, 16 donors (6.5%) from urine cultures, and 7 donors (2.8%) from bile cultures.

Microorganisms in donor cultures

All positive bacterial cultures derived from donors are described in Table 1. A total of 21 bacterial species were identified, including 9 Gram-positive, 11 Gram-negative, and 1 Gram-variable. Among these, the three most common bacteria were *Klebsiella pneumoniae* (*n*=34), *Staphylococcus aureus* (*n*=32), and *Escherichia coli* (*n*=13). *Coagulase-negative Staphylococcus* was the first ranked bacterium found in the blood cultures of 7 donors, and *Escherichia coli* was the most common bacterium found in the urine cultures of 8 donors. *Klebsiella pneumoniae* was isolated from 32 donor sputum cultures and 2 donor bile cultures. Additionally, *Pseudomonas aeruginosa*, a relative common nosocomial species, was cultivated from 10 donor sputum cultures.

Recipient outcomes

Among the 285 DDLTs, 98 recipients (Group I) obtained grafts from 78 donors with positive bacterial cultures, while the remaining 187 recipients (Group II) were

transplanted with grafts from 170 donors who had no evidence of bacterial infection. The clinical characteristics of recipients are summarized and compared in Table 2. The majority of clinical features were similar between the two groups. However, the mean recipient age in Group I was significantly greater than that of Group II recipients ($p = 0.002$), and a significantly higher ratio of Group II recipients received whole liver grafts for transplantation ($p = 0.0002$). Moreover, group I patients had relative higher ratio of comorbidity as compared with Group II patients at the time of transplantation. ($p = 0.0414$) Importantly, the rates of bacterial growth from blood cultures and hospital mortality within 30 days after LT were not significantly different between the two groups. Overall, 159 (55.8%) patients were still alive by the end of the study, including 57 (58.2%) patients in Group I and 102 (54.5%) patients in Group II.

In Group I, only one recipient (1.02%) had *Acinetobacter baumannii* detected in a blood culture after LT, which was the same bacterium cultured from the donor's sputum prior to organ donation. The recipient was indicated for LT due to hepatitis B virus-related end stage liver cirrhosis, and obtained a right liver graft from a split liver donation. However, no evidence of *Acinetobacter baumannii* growth was noted in the blood culture in the other recipient who received a left liver graft from the same donor. The groups of patients who obtained grafts from donor with and without bacterial

infection were compared and similar outcomes were found between the two groups (Fig. 3, $p = 0.9746$). The analysis of the survival curves showed that the overall survival rates at one and three years were 73.5% and 69.2% in Group I recipients, while the corresponding values were 68.8% and 62.4% in Group II recipients.

Discussion

Although LT is currently considered the definitive treatment for individuals with end-stage liver disease, unexpected transmission of infections from the donor to the recipient remains a major concern. Although rare, complication related to donor-derived infectious disease are associated with significant morbidity and mortality. (3, 5-7) Among the types of donor-derived infections, bacterial transmission from the donor could result in bacteremia immediately after transplantation and lead to lethal complications. However, deceased donors are extremely rare in Oriental countries, and the organ shortage for LT is exceptionally large as compared with Western countries.(8, 9) Therefore, every donor should be carefully judged for organ transplantation. This study analyzed donors in terms of bacterial infections in the setting of scarce organ donation. The results show that the incidence of donor-transmitted bacterial infections was very low, suggesting that donors with a

bacterial infection should not be excluded as organ donors for LT.

Generally, bacteria are the most common cause of infections in LT recipients. However, opportunistic infections are generally uncommon in the first 1-4 weeks after transplantation, depending on the recipient's net state of immunity. Thus, unexplained early infections in this period are generally associated with surgery-related complications or donor-derived infections. This study examined all recipient blood cultures for bacteria within 30 days after LT to match the donor's bacterial infection. In line with previous reports, the incidence of possible bacterial transmission from the donor was very low.(10, 11) Only one recipient's blood culture had the same bacterium as the donor, and accounted for only 1.02% of all recipients in the current study.

Acinetobacter baumannii is a typical Gram-negative bacterium that can be an opportunistic pathogen affecting patients with compromised immune systems.(12, 13) However, the recipient who obtained the left liver graft from the same donor had no evidence of this bacterium in their blood cultures after LT. Therefore, the recipient's pathogen could be a hospital-derived nosocomial infection instead of transmission from donor. Meanwhile, liver grafts are usually flushed with organ preserving solution during organ procurement, and re-perfused with more than 1500 ml/min of

the recipient's blood after graft implantation. As such, bacteria within the liver graft are likely to be diluted by these process, and the chance of donor-derived bacterial infection in the recipient is very low.

However, the possibility of potential donor with severe bacterial infections such as *Acinetobacter baumannii*, v*ancomycin resistance Escherichia coli (VRE)*, or *multi-drug resistant bacteria* might be existed. These antimicrobial resistance bacteria were mostly detected in patients with severe illness or compromised immune systems, and thus they might be unacceptable for organ donation because of poor general condition. Although the usage of organs from donors infected with drug-resistance bacteria remains uncertain, the urgent demand for organs perhaps would led to the use of organs from these donors for specific recipients based on the urgency of the need for transplantation. Nonetheless, the study was limited by its small number of patients, in which the impact of the drug-resistance bacteria on the outcome of DDLT could not be truly reflected. Therefore, further information from a larger cohort study to clarify the influence of drug-resistance bacteria on organs transplantation is required in the future.

Our data are similar to previous reports showing that the highest positive rate of bacterial culture of the donor was from sputum cultures.(11, 14) The most common

pathogens cultivated from bronchial aspirates of the donors in this study were *Klebsiella pneumoniae* and *Staphylococcus aureus*. Both pathogens are members of the normal flora of the body, and are frequently found in the respiratory tract and skin.(15, 16) *Klebsiella* infections are mostly seen in people with a weakened immune system or a nosocomial infection, and *Staphylococcus aureus* is not always pathogenic. Additionally, *Escherichia coli* was the most common pathogen found in the urine cultures of our donor, which might be related to either translocation from the gastrointestinal tract or contamination with feces. Therefore, culture results from donors that show these pathogens could be ignored so the donors are not excluded from organ donation.

Importantly, each potential donor should be comprehensively screened for medical conditions that may affect the recipient, which might include the presence of transmissible disease, malignancies, or any other known condition that may be transmitted by the donor organ. However, it is currently impossible to screen potential donors for all potential pathogens during the narrow timeframe of the organ donation process. Specifically, bacterial cultures of potential donors take time and may not provide results prior to organ procurement for transplantation. Likewise, a donor may have a bacterial infection that has been appropriately treated. Under such circumstances, treatment of the recipient for the recognized infection immediately

after transplantation might be satisfactory.

The preventive strategy of universal prophylaxis is mainly rely on the clinical status of the recipient. Generally, microorganisms transmitted from donors is not likely to cause infectious complications in every recipient, and the risk of infection is mostly associated with the patient's net state of immunity. Therefore, antimicrobial prophylaxis should be adjusted based on the severity of recipient's illness, individual exposures, and hospital epidemiology. Additionally, antimicrobial prophylaxis should also be adjusted according to identified microorganisms from donors. As a result, it can provide adequate coverage of bacterial infections cultured from donor and prevent infectious complication related to transmission of donor-derived infectious diseases.

Conclusions

Although the study is limited by its retrospective entity in a single transplantation center with a small number of patients, several marked observation might be helpful in clinical practice. Additionally, available organ donor numbers lag behind current and future needs, and this organ shortage has thus forced clinicians to expand the donor pool by using donors with the risk of transmitting infectious diseases. The annual deceased organ donation rate has recently increased to 12.3 per million population in Taiwan, but the number of DDLTs is still not satisfactory, with an

average of 100 cases per year.(17) Many other counties may also encounter this situation regarding deceased donor organ transplantation and LT. As a result, a bacterial infection in the donor should not preclude the use of organs for transplantation. Moreover, the possibility of bacterial transmission from the donor seems to extremely low considering fluid dilution and the non-specific culture results.

Author contributions:
Study concept, design and drafting the manuscript: Kun-Ming Chan
Acquisition of data: Kun-Ming Chan, Tsung-Han Wu, Chih-Hsien Cheng, Chen-Fang Lee, Ting-Jung Wu, Hong-Shiue Chou, Wei-Chen Lee
Critical revision of the manuscript for important intellectual content: Kun-Ming Chan, Wei-Chen Lee

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Patient consents: Obtained.

Ethics approval: The Institutional Review Board of Chang Gung Memorial Hospital (Approval No.: 98-3794B)

Data sharing statement: No additional data available.

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Table 1. Microorganisms cultured from donors.

Micro-organisms	Bacterial cultures				Total
	Sputum	Urine	Blood	Bile	
Gram-positive bacteria					
Staph.aureus	31	–	1	–	32
coagulase-negative staphylococcus	–	–	7	1	8
Enterococcus faecalis	–	5	1	–	6
staphylococcus	1	–	2	–	3
Streptococcus pneumoniae	3	–	–	–	3
Staph.epidermidis	–	1	1	–	2
Aerococcus	–	–	–	1	1
Enterococcus faecium	–	–	–	1	1
Propionibacterium acnes	–	–	–	1	1
Gram-negative bacteria					
Klebsiella pneumoniae	32	–	–	2	34
Escherichia coli	4	8	–	1	13
Pseudomonas aeruginosa	10	2	–	–	12
Haemophilus influenzae	8	–	–	–	8
Enterobacter cloacae	4	3	–	–	7
Acinetobacter baumannii	5	–	1	–	6
Stenotrophomonas maltophilia	2	2	1	1	6
Enterobacter aerogenes	4	–	1	–	5
Veillonella sp	–	–	2	–	2
Proteus mirabilis	2	–	–	–	2
Serratia marcescens	2	–	–	–	2
other					
Gardnerella vaginalis	–	1	–	–	1

Number represent number of patients

Table 2. Clinical characteristics of patients with deceased donor liver transplantation.

Characteristics	Donor with positive bacterial cultures		*p* value
	Group I: Yes, *n*=98	Group II: No, *n*=187	
Age, median (range)	52 (33 – 65)	48 (1 – 67)	0.002
Sex (Male:Female)	77:21	132:55	0.160
Hepatitis status			0.403
Hepatitis B positive	51 (52.0%)	110 (58.8%)	
Hepatitis C positive	21 (21.4%)	27 (14.5%)	
Hepatitis B, C positive	3 (3.1%)	9 (4.8%)	
None	23 (23.5%)	41 (21.9%)	
Comorbidity			0.0414
Diabetic Mellitus	13 (13.3%)	14 (7.5%)	
Hypertension	12 (12.2%)	12 (6.4%)	
Chronic renal disease	5 (5.1%)	5 (2.7%)	
Heart disease	3 (3.1%)	0	
Others	3 (3.1%)	6 (3.2%)	
No	72 (73.5%)	157 (84.0%)	
Indication of LT			0.147
Alcoholic Liver cirrhosis	16 (16.3%)	10 (5.4%)	
Virus-related liver cirrhosis	40 (40.8%)	98 (52.4%)	
Hepatocellular carcinoma	32 (32.7%)	46 (24.6%)	
Others	10 (10.2%)	33 (17.6%)	
MELD score, median (range)	21 (7 – 40)	23 (7 – 40)	0.673
Type of grafts			0.0002
Whole liver graft	53 (54.1%)	142 (75.9%)	
Partial liver graft*	45 (45.9%)	45 (24.1%)	
Blood culture after LT (30days)			0.173
Positive bacterial growth	11 (11.2%)	12 (6.4%)	
Negative bacterial growth	87 (88.8%)	175 (93.6%)	
Patient outcomes			
Hospital Mortality (30days)	11 (11.2%)	23 (12.3%)	0.849
Graft dysfunction	0	4 (2.1%)	
Postoperative hemorrhage	2 (2.0%)	5 (2.7%)	
Severe bacterial infections	4 (4.1%)	8 (4.3%)	
Acute rejections	3 (3.1%)	4 (2.1%)	
Others	2 (2.0%)	2 (1.1%)	
Death	30 (30.6%)	62 (33.2%)	
Alive	57 (58.2%)	102 (54.5%)	

LT, liver transplantation; MELD, Model for End-stage Liver Disease. *partial liver grafts

included split liver and reduced size liver grafts.

Figure legend

Figure 1. Flow diagram of organ donors and liver transplantations assessed in this study.

Figure 2. The rate of positive bacterial cultures in donors.

Figure 3. Comparison of cumulative overall survival for the patients showing no significant difference between the two groups. Group I (⋯), Group II (—).

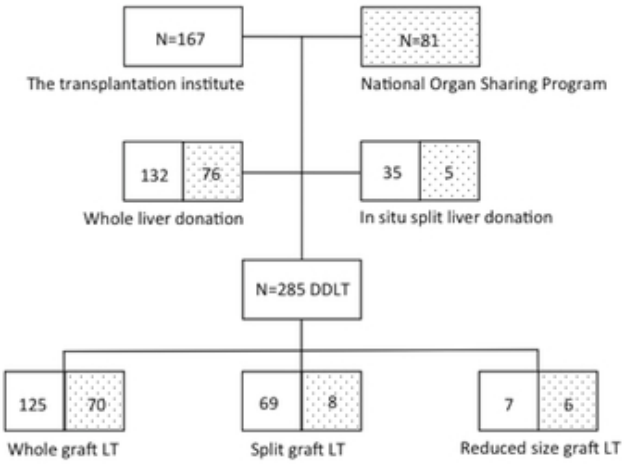

Figure 1

45x25mm (300 x 300 DPI)

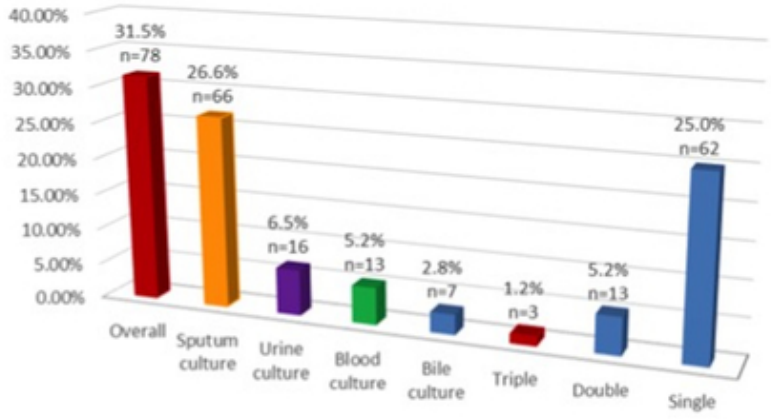

Figure 2

44x24mm (300 x 300 DPI)

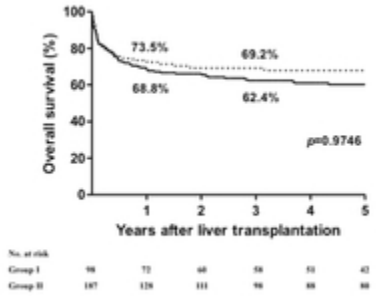

Figure 3

30x17mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5,6
Study design	#4	Present key elements of study design early in the paper	5,6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6,7

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	8,9
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8,9
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8,9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8,9
	#12b	Describe any methods used to examine subgroups and interactions	8,9
	#12c	Explain how missing data were addressed	See note 1
	#12d	If applicable, explain how loss to follow-up was addressed	See note 2
	#12e	Describe any sensitivity analyses	See note 3
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	See note

			4
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9-11
	#14b	Indicate number of participants with missing data for each variable of interest	See note 5
	#14c	Summarise follow-up time (eg, average and total amount)	11
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See note 6
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	16

the present article is based

Author notes

1. n/a, no missing data
2. n/a, no loss follow-up patient
3. n/a, not applicable
4. 6, figure 1
5. n/a, no missing data
6. n/a, not applicable

BMJ Open

Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study in Taiwan

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Title: Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study in Taiwan

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Abstract

Objective: The shortage of available donor organs is an unsolvable concern leading to an expansion in the donor criteria for organ transplantation. Here, we describe our experience and assess the outcomes in recipients who obtained a graft from a donor with bacterial infections in deceased donor liver transplantation (DDLT).

Methods: All DDLTs between January 1991 and February 2017 were retrospectively reviewed. Patients were categorized into two groups based on recipients who obtained a graft from a donor with (Group I) or without (Group II) evidence of bacterial infections. Outcomes and bacterial infections were compared between the two groups of recipients.

Results: Overall, a total of 285 DDLTs were performed from 248 donors consisting of 48 split liver grafts and 208 whole liver grafts. Of those, 98 recipients (Group I, 34.3%) were transplanted with a graft from 78 donors with positive bacterial cultures. Donor sputum cultures had the highest rate of positive bacterial growth, accounting for 26.6% of donors. Overall survival was not significantly different between the two groups. (p=0.9746) The overall survival rates at one and three years were 73.5% and 69.2% in the Group I recipients *versus* 68.8% and 62.4% in the Group II recipients. Importantly, no hospital mortality was related to donor-derived bacterial infections.

Conclusion: Transmission of bacteria from the donor to the recipient is infrequent in DDLT. Therefore, potential donors with positive bacterial infections should not be excluded for organ transplantation in order to increase organ availability and ameliorate the organ shortage.

Keywords: deceased donor; bacterial infection; transmission; liver transplantation; outcomes

Strengths and limitations of this study

1. The shortage of deceased organ donors is stringent in Oriental Countries as compared with Western Countries, and thus every donor should be carefully judged for organ transplantation in order to achieve greatest effectiveness.

2. This study enrolled 285 deceased donor liver transplantation in the setting of scarce organ donation, and analyzed the influence of donors with evidence of bacterial infections on liver transplantation.

3. The results show that the incidence of donor-transmitted bacterial infections was very low, suggesting that donors with a bacterial infection should not be excluded as

organ donors for liver transplantation.

4. The study is limited by its retrospective entity in a single transplantation center with a small number of patients.

Introduction

Organ transplantation is a promising alternative for the treatment of many end-stage diseases. However, the discrepancy between organ demand and donor availability is currently an unsolvable concern. Therefore, expanded donor criteria including older donors, circulatory death donors, or donors with mild diseases and so forth are increasingly used as donors for organ transplantation. Subsequently, there is a high possibility of the transmission of unwanted infectious diseases following organ donation. Infectious microbes including viruses, bacteria, parasites and fungi that are present in organ donors have the potential to be transmitted to the transplant recipient.(1-3) The influence of these donor-transmitted infectious diseases on the outcome of organs transplantation could be immediately after transplantation or lasting several years afterward. However, the study focus on assessing donor with bacterial infection and related impact immediately after liver transplantation.

Any active bacterial infection in the donor may result in a lethal complication immediately after transplantation if bacteria are transmitted to the recipient during organ transplantation. Thus, the majority of transplantation surgeons are reluctant to transplant organs known to be infected by active bacteria. Specifically, the shortage of deceased donor is very stringent particularly in Oriental countries. In this study,

donors with bacterial infections were analyzed to assess the influence of an infected donor on the outcome of deceased donor liver transplantation (DDLT). These results might provide additional information for the selection of deceased donors for liver transplantation (LT).

Methods

Patients

A total of 285 consecutive DDLTs were performed during the period between January 1991 and February 2017 at the Transplantation Institute. All medical records of donors and recipients were retrospectively reviewed under the approval from the Institutional Review Board of Chang Gung Memorial Hospital. Of all LT, liver grafts were procured from 248 donors including 81 donors from the national organ sharing program and 167 donations from the institute. No executed prisoner organs were used in this study. Liver graft donations and transplantations are illustrated in Figure 1. Overall, 40 donors underwent split liver donation, and whole liver grafts were procured from the 208 donors. Among whole liver donors, 13 donors had reduced size liver grafts from a partial liver resected *ex vivo* in order to be implanted in recipients with a relatively small abdominal cavity. Written informed consent was obtained from

all patients included.

Donor survey

All potential donors were thoroughly checked by laboratory tests for hepatitis B and C virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), toxoplasmosis and syphilis. Generally, chest radiography and ultrasonography of the heart, liver and kidney would be routinely performed prior to the donation of solid organs. With regard to the assessment of bacterial infection, serial samples including bronchial aspirates, urine and blood were obtained for culture before organs donation.

Generally, the potential donor should be hemodynamic stable with acceptable cardiopulmonary function, absence of sepsis or uncontrollable bacterial infection and without malignant neoplasm contraindicated for donation. Donor with virus including hepatitis B, C virus, and HIV (after November 2016) were not contraindicated for organs donation, but could be transplanted to recipient with same viral status. For liver donation, the liver functional reserve of donor should be acceptable and less than 50% of hepatic parenchyma with steatosis. If the donor was eligible for organ donation, transplantation surgeons would proceed to organ procurement after the determination of brain death by specialists. There is no organs obtained from non-

heart beating donor in this study.

The decision to perform split liver grafts in two adult recipients was based on preoperative hepatic sonography and an intraoperative assessment of the liver graft. Transection of the hepatic parenchyma for split liver grafts was all performed *in situ* as previously described.(4) Importantly, bile was routinely obtained through the common bile duct for bacterial culture before flushing the biliary tree during liver graft procurement from all donors.

Liver transplantation recipients

All graft implantations were performed using standard techniques without venovenous bypass. Generally, prophylactic antibiotics were usually administered for all recipients after transplantation unless the susceptibility profile required specific antibiotics prior to transplantation. The selection of prophylactic antibiotics was based on the illness of recipients, in which third-generation cephalosporins was given to recipients with Model For End-Stage Liver Disease (MELD) scores less than 20; a combination of vancomycin and imipenem/cilastatin was administered to recipients with MELD scores above 20. Additionally, antibiotic treatment specific to the recognized microorganisms from donor were also administered after transplantation based on the result of donor's bacterial culture. The use of antifungal prophylaxis was

optional for recipients who had high risk of fungal infections such as longer hospitalization before transplantation, longer operation time, massive blood loss and blood transfusion during the operation. The immunosuppressive regimen for recipients after transplantation mainly consisted of a combination of methylprednisolone, tacrolimus and mycophenolate mofetil, and adjusted based on the clinical assessment of the recipient.

Outcomes and statistical analysis

Recipients were categorized into two groups: Group I consisted of recipients transplanted with a graft procured from a donor with a positive bacterial culture, and Group II included recipients who obtained a graft from a donor without evidence of bacterial infection. Bacterial infection was intensively monitored using samples from the blood, drainage tubes and catheters for all recipients after LT. Microorganisms that grew in all cultures within 30 days after LT were recorded and assessed for bacterial infection transmission from donor. The recipient's outcome measure was overall survival (OS), which was calculated from the date of LT to the date of death or the end of this study. Survival curves were constructed by the Kaplan-Meier method, and further compared by the log rank test. All variables were assessed for multivariate analyses using the Cox hazards regression model. Comparison of

continuous variables were performed by Student's t test, and categorical variables were compared by the chi-square or Fisher's exact test as appropriate. All data were analyzed using the statistical software SPSS version 20.0 (IBM Inc., Armonk, NY, USA) for Windows. A *p*-value of < 0.05 was defined as statistically significant.

Patient and public involvement statement

This study analyzed a retrospective data review. There was no patient or public involvement in this study including in the design, recruitment, and conduct of the study.

Results

Donor features

All donors were donation after brain death; the 248 donors consisted of 174 males and 74 females. The median age of the donors was 40 years old, and ranged from 9 to 75 years old. The major causes of brain death were cerebrovascular accidents in 137 donors (55.2%) and head injury in 48 donors (19.4%). The median duration of stay in the intensive care unit before donation was 3 days (ranging from 1 to 95 days). Overall, 78 donors (31.5%) had positive bacterial culture samples, in which 3 (1.2%)

of them had triple site positives, 13 (5.2%) had double site positives, and 62 (25%) had only single site positive (Fig. 2). Most positive bacterial cultures were from bronchial aspirates of sputum, which were noted in 66 donors that accounted for 26.6% of all donors and 84.6% among donors with positive bacterial infections. Additionally, bacterial growth was detected from blood cultures in 13 donors (5.2%), from urine cultures in 16 donors (6.5%), and from bile cultures in 7 donors (2.8%).

Microorganisms in donor cultures

All positive bacterial cultures derived from donors are described in Table 1. A total of 21 bacterial species were identified, including 9 Gram-positive, 11 Gram-negative, and 1 Gram-variable. Among these, the three most common bacteria were *Klebsiella pneumoniae* (*n*=34), *Staphylococcus aureus* (*n*=32), and *Escherichia coli* (*n*=13). *Coagulase-negative Staphylococcus* was the first ranked bacterium found in the blood cultures of 7 donors, and *Escherichia coli* was the most common bacterium found in the urine cultures of 8 donors. *Klebsiella pneumoniae* was isolated from 32 donor sputum cultures and 2 donor bile cultures. Additionally, *Pseudomonas aeruginosa*, a relative common nosocomial species, was cultivated from 10 donor sputum cultures.

Recipient outcomes

Among the 285 DDLTs, 98 recipients (Group I) obtained grafts from 78 donors with

positive bacterial cultures, while the remaining 187 recipients (Group II) were transplanted with grafts from 170 donors who had no evidence of bacterial infection. The clinical characteristics of recipients are summarized and compared in Table 2. The majority of clinical features were similar between the two groups. However, the mean recipient age in Group I was significantly greater than that of Group II recipients ($p = 0.002$), and a significantly higher ratio of Group II recipients received whole liver grafts for transplantation ($p = 0.0002$). Moreover, group I patients had relative higher ratio of comorbidity as compared with Group II patients at the time of transplantation. ($p = 0.0414$) Importantly, the rates of bacterial growth from blood cultures and hospital mortality within 30 days after LT were not significantly different between the two groups. Overall, 159 (55.8%) patients were still alive by the end of the study, including 57 (58.2%) patients in Group I and 102 (54.5%) patients in Group II.

In Group I, only one recipient (1.02%) had *Acinetobacter baumannii* detected in a blood culture after LT, which was the same bacterium cultured from the donor's sputum prior to organ donation. The recipient was indicated for LT due to hepatitis B virus-related end stage liver cirrhosis, and obtained a right liver graft from a split liver donation. However, no evidence of *Acinetobacter baumannii* growth was noted in the blood culture in the other recipient who received a left liver graft from the same

donor. Patients who obtained grafts from donor with and without bacterial infection were compared, and similar outcomes were found between the two groups (Fig. 3, p = 0.9746). The analysis of the survival curves showed that the overall survival rates at one and three years were 73.5% and 69.2% in Group I recipients, while the corresponding values were 68.8% and 62.4% in Group II recipients. The hazard ratio (HR) of donor with evidence of bacterial infection was 1.01 [p = 0.956, 95% confidence interval (CI) = 0.69-1.47] for overall survival after transplantation, and the adjusted HR were 0.80 (p = 0.310, 95% CI= 0.52-1.23) after adjusted for gender, age, and comorbidity.

Additionally, a propensity score matching was performed to minimize the influence of confounding factors between the two groups. According to the matching analysis, there was also no significant differences between the two groups in terms of overall survival. (Fig. 4, p = 0.3443) The 1- and 3-year OS was 73.5% and 62.2% for patients in the group I, and 69.2% and 56.1%, respectively for patients in the group II. Moreover, multivariate regression analysis showed that the presence of donor with bacterial infection was not a significant prognostic factor affecting recipient's outcome after liver transplantation as well. (Supplemental table 1).

Discussion

Although LT is currently considered the definitive treatment for individuals with end-stage liver disease, unexpected transmission of infections from the donor to the recipient remains a major concern. Although rare, complication related to donor-derived infectious disease are associated with significant morbidity and mortality. (3, 5-7) Among the types of donor-derived infections, bacterial transmission from the donor could result in bacteremia immediately after transplantation and lead to lethal complications. However, deceased donors are extremely rare in Oriental countries, and the organ shortage for LT is exceptionally large as compared with Western countries.(8, 9) Therefore, every donor should be carefully judged for organ transplantation. This study analyzed donors in terms of bacterial infections in the setting of scarce organ donation. The results show that the incidence of donor-transmitted bacterial infections was very low, suggesting that donors with a bacterial infection should not be excluded as organ donors for LT.

Generally, bacteria are the most common cause of infections in LT recipients. However, opportunistic infections are generally uncommon in the first 1-4 weeks after transplantation, depending on the recipient's net state of immunity. Thus, unexplained early infections in this period are generally associated with surgery-related

complications or donor-derived infections. This study examined all recipient blood cultures for bacteria within 30 days after LT to match the donor's bacterial infection. In line with previous reports, the incidence of possible bacterial transmission from the donor was very low.(10, 11) Only one recipient's blood culture had the same bacterium as the donor, and accounted for only 1.02% of all recipients in the current study.

Acinetobacter baumannii is a typical Gram-negative bacterium that can be an opportunistic pathogen affecting patients with compromised immune systems.(12, 13) However, the recipient who obtained the left liver graft from the same donor had no evidence of this bacterium in their blood cultures after LT. Therefore, the recipient's pathogen could be a hospital-derived nosocomial infection instead of transmission from donor. Meanwhile, liver grafts are usually flushed with organ preserving solution during organ procurement, and re-perfused with more than 1500 ml/min of the recipient's blood after graft implantation. As such, bacteria within the liver graft are likely to be diluted by these process, and the chance of donor-derived bacterial infection in the recipient is very low.

However, the possibility of potential donor with severe bacterial infections such as *Acinetobacter baumannii*, v*ancomycin resistance Escherichia coli (VRE)*, or *multi-*

drug resistant bacteria might be existed. These antimicrobial resistance bacteria were mostly detected in patients with severe illness or compromised immune systems, and thus they might be unacceptable for organ donation because of poor general condition. Although the usage of organs from donors infected with drug-resistance bacteria remains uncertain, the urgent demand for organs perhaps would led to the use of organs from these donors for specific recipients based on the urgency of the need for transplantation. Nonetheless, the study was limited by its small number of patients, in which the impact of the drug-resistance bacteria on the outcome of DDLT could not be truly reflected. Therefore, further information from a larger cohort study to clarify the influence of drug-resistance bacteria on organs transplantation is required in the future.

Our data are similar to previous reports showing that the highest positive rate of bacterial culture of the donor was from sputum cultures.(11, 14) The most common pathogens cultivated from bronchial aspirates of the donors in this study were *Klebsiella pneumoniae* and *Staphylococcus aureus*. Both pathogens are members of the normal flora of the body, and are frequently found in the respiratory tract and skin.(15, 16) *Klebsiella* infections are mostly seen in people with a weakened immune system or a nosocomial infection, and *Staphylococcus aureus* is not always pathogenic. Additionally, *Escherichia coli* was the most common pathogen found in

the urine cultures of our donor, which might be related to either translocation from the gastrointestinal tract or contamination with feces. Therefore, culture results from donors that show these pathogens could be ignored so the donors are not excluded from organ donation.

Importantly, each potential donor should be comprehensively screened for medical conditions that may affect the recipient, which might include the presence of transmissible disease, malignancies, or any other known condition that may be transmitted by the donor organ. However, it is currently impossible to screen potential donors for all potential pathogens during the narrow timeframe of the organ donation process. Specifically, bacterial cultures of potential donors take time and may not provide results prior to organ procurement for transplantation. Likewise, a donor may have a bacterial infection that has been appropriately treated. Under such circumstances, treatment of the recipient for the recognized infection immediately after transplantation might be satisfactory.

The preventive strategy of universal prophylaxis is mainly rely on the clinical status of the recipient. Generally, microorganisms transmitted from donors is not likely to cause infectious complications in every recipient, and the risk of infection is mostly associated with the patient's net state of immunity. Therefore, antimicrobial

prophylaxis should be adjusted based on the severity of recipient's illness, individual exposures, and hospital epidemiology. Additionally, antimicrobial prophylaxis should also be adjusted according to identified microorganisms from donors. As a result, it can provide adequate coverage of bacterial infections cultured from donor and prevent infectious complication related to transmission of donor-derived infectious diseases.

Conclusions

Although the study is limited by its retrospective entity in a single transplantation center with a small number of patients, several marked observation might be helpful in clinical practice. Additionally, available organ donor numbers lag behind current and future needs, and this organ shortage has thus forced clinicians to expand the donor pool by using donors with the risk of transmitting infectious diseases. The annual deceased organ donation rate has recently increased to 12.3 per million population in Taiwan, but the number of DDLTs is still not satisfactory, with an average of 100 cases per year.(17) Many other counties may also encounter this situation regarding deceased donor organ transplantation and LT. As a result, a bacterial infection in the donor should not preclude the use of organs for transplantation. Moreover, the possibility of bacterial transmission from the donor seems to extremely low considering fluid dilution and the non-specific culture results.

Author contributions:
Study concept, design and drafting the manuscript: Kun-Ming Chan
Acquisition of data: Kun-Ming Chan, Tsung-Han Wu, Chih-Hsien Cheng, Chen-Fang Lee, Ting-Jung Wu, Hong-Shiue Chou, Wei-Chen Lee
Critical revision of the manuscript for important intellectual content: Kun-Ming Chan, Wei-Chen Lee

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Patient consents: Obtained.

Ethics approval: The Institutional Review Board of Chang Gung Memorial Hospital

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Data sharing statement: No additional data available.

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Table 1. Microorganisms cultured from donors.

Micro-organisms	Bacterial cultures				Total
	Sputum	Urine	Blood	Bile	
Gram-positive bacteria					
Staph.aureus	31	–	1	–	32
coagulase-negative staphylococcus	–	–	7	1	8
Enterococcus faecalis	–	5	1	–	6
staphylococcus	1	–	2	–	3
Streptococcus pneumoniae	3	–	–	–	3
Staph.epidermidis	–	1	1	–	2
Aerococcus	–	–	–	1	1
Enterococcus faecium	–	–	–	1	1
Propionibacterium acnes	–	–	–	1	1
Gram-negative bacteria					
Klebsiella pneumoniae	32	–	–	2	34
Escherichia coli	4	8	–	1	13
Pseudomonas aeruginosa	10	2	–	–	12
Haemophilus influenzae	8	–	–	–	8
Enterobacter cloacae	4	3	–	–	7
Acinetobacter baumannii	5	–	1	–	6
Stenotrophomonas maltophilia	2	2	1	1	6
Enterobacter aerogenes	4	–	1	–	5
Veillonella sp	–	–	2	–	2
Proteus mirabilis	2	–	–	–	2
Serratia marcescens	2	–	–	–	2
other					
Gardnerella vaginalis	–	1	–	–	1

Number represent number of patients

Table 2. Clinical characteristics of patients with deceased donor liver transplantation.

Characteristics	Donor with positive bacterial cultures		*p* value
	Group I: Yes, *n*=98	Group II: No, *n*=187	
Age, median (range)	52 (33 – 65)	48 (1 – 67)	0.002
Sex (Male:Female)	77:21	132:55	0.160
Hepatitis status			0.403
Hepatitis B positive	51 (52.0%)	110 (58.8%)	
Hepatitis C positive	21 (21.4%)	27 (14.5%)	
Hepatitis B, C positive	3 (3.1%)	9 (4.8%)	
None	23 (23.5%)	41 (21.9%)	
Comorbidity			0.0414
Diabetic Mellitus	13 (13.3%)	14 (7.5%)	
Hypertension	12 (12.2%)	12 (6.4%)	
Chronic renal disease	5 (5.1%)	5 (2.7%)	
Heart disease	3 (3.1%)	0	
Others	3 (3.1%)	6 (3.2%)	
No	72 (73.5%)	157 (84.0%)	
Indication of LT			0.147
Alcoholic Liver cirrhosis	16 (16.3%)	10 (5.4%)	
Virus-related liver cirrhosis	40 (40.8%)	98 (52.4%)	
Hepatocellular carcinoma	32 (32.7%)	46 (24.6%)	
Others	10 (10.2%)	33 (17.6%)	
MELD score, median (range)	21 (7 – 40)	23 (7 – 40)	0.673
Type of grafts			0.0002
Whole liver graft	53 (54.1%)	142 (75.9%)	
Partial liver graft*	45 (45.9%)	45 (24.1%)	
Blood culture after LT (30days)			0.173
Positive bacterial growth	11 (11.2%)	12 (6.4%)	
Negative bacterial growth	87 (88.8%)	175 (93.6%)	
Patient outcomes			
Hospital Mortality (30days)	11 (11.2%)	23 (12.3%)	0.849
Graft dysfunction	0	4 (2.1%)	
Postoperative hemorrhage	2 (2.0%)	5 (2.7%)	
Severe bacterial infections	4 (4.1%)	8 (4.3%)	
Acute rejections	3 (3.1%)	4 (2.1%)	
Others	2 (2.0%)	2 (1.1%)	
Death	30 (30.6%)	62 (33.2%)	

Alive	57 (58.2%)	102 (54.5%)

LT, liver transplantation; MELD, Model for End-stage Liver Disease. *partial liver grafts included split liver and reduced size liver grafts.

Figure legend

Figure 1. Flow diagram of organ donors and liver transplantations assessed in this study.

Figure 2. The rate of positive bacterial cultures in donors.

Figure 3. Comparison of cumulative overall survival for the patients show no significant difference between the two groups. Kaplan–Meier overall survival curves of patients. (p = 0.9746) Group I (⋯), Group II (—).

Figure 4. Comparison of cumulative overall survival for the patients show no significant difference between the two groups. Kaplan–Meier overall survival curves of patients after propensity score matching. (p = 0.3443) Group I (⋯), Group II (—).

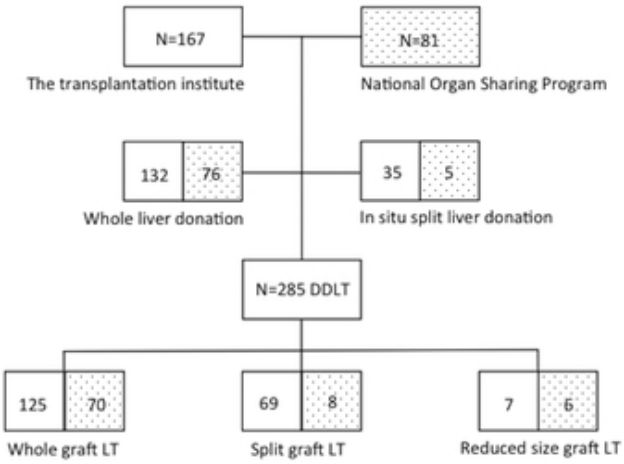

Figure 1

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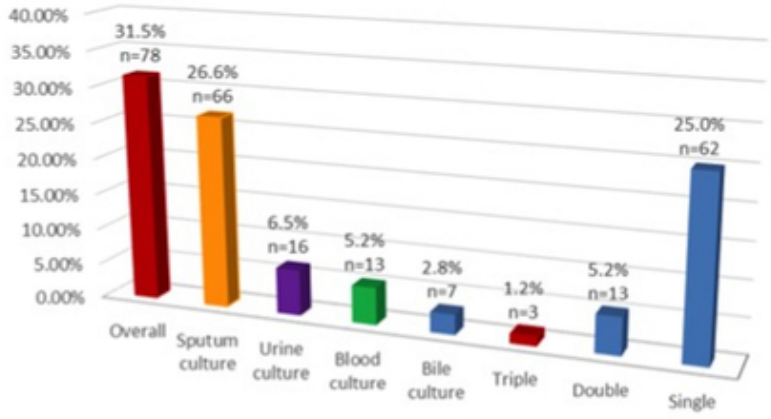
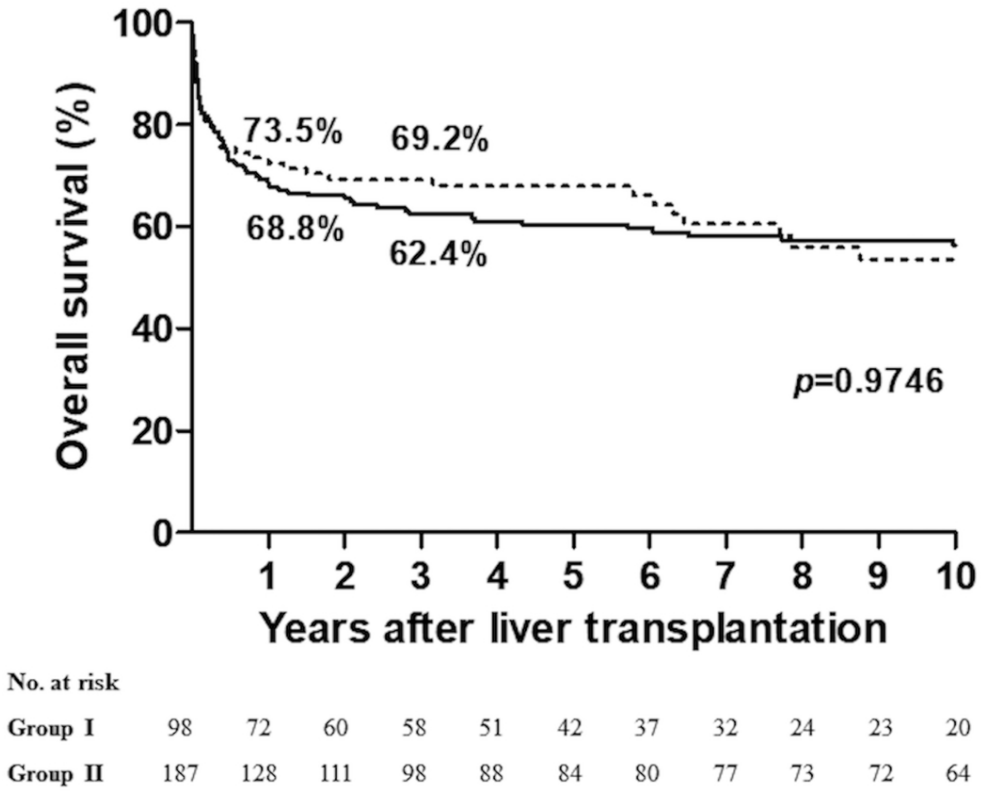


Figure 2

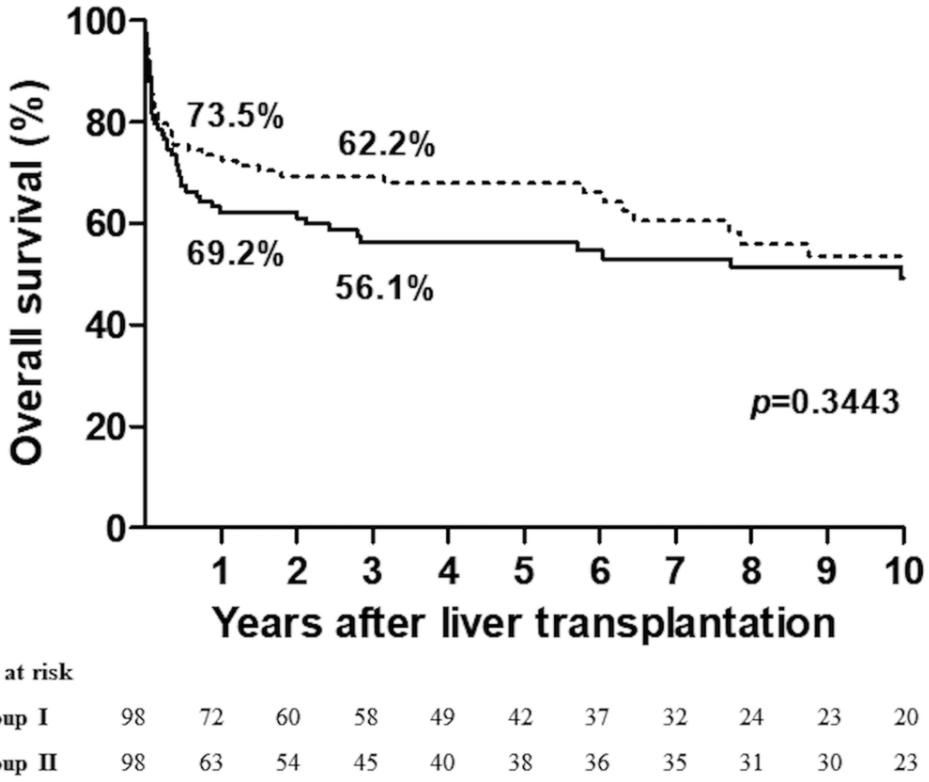
44x24mm (300 x 300 DPI)



No. at risk											
Group I	98	72	60	58	51	42	37	32	24	23	20
Group II	187	128	111	98	88	84	80	77	73	72	64

Figure 3A

90x78mm (300 x 300 DPI)



No. at risk										
Group I	98	72	60	58	49	42	37	32	24	23	20
Group II	98	63	54	45	40	38	36	35	31	30	23

Figure 3B

90x80mm (300 x 300 DPI)

Supplemental table 1. Multivariate analyses of clinical features affecting overall survival after liver transplantation.

Factors	Multivariate analysis		
	Hazard Ratio	95% Confidence Interval	*p* value
Age (years)			
≤55 *versus* >55	0.99	0.63 – 1.56	0.974
Gender			
Male *versus* Female	1.17	0.74 – 1.85	0.512
Hepatitis virus			
Hepatitis B positive	0.76	0.45 – 1.29	0.307
Hepatitis C positive	1.27	0.70 – 2.30	0.427
Hepatitis B, C positive	0.48	0.14 – 1.63	0.240
Comorbidity			
Yes *versus* No	1.29	0.71 – 2.35	0.406
Graft type			
Whole liver *versus* partial liver	1.56	1.01 – 2.40	0.043
Bacterial cultures of donor			
Positive *versus* Negative	0.80	0.52 – 1.23	0.310
MELD score			
> 20 versus ≤ 20	1.01	0.99 – 1.04	0.132
Blood cultures after liver transplantation (30 days)			
Positive *versus* Negative	1.52	0.85 – 2.74	0.160

MELD: model for end-stage liver disease

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5,6
Study design	#4	Present key elements of study design early in the paper	5,6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6,7

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	8,9
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8,9
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8,9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8,9
	#12b	Describe any methods used to examine subgroups and interactions	8,9
	#12c	Explain how missing data were addressed	See note 1
	#12d	If applicable, explain how loss to follow-up was addressed	See note 2
	#12e	Describe any sensitivity analyses	See note 3
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	See note

			4
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9-11
	#14b	Indicate number of participants with missing data for each variable of interest	See note 5
	#14c	Summarise follow-up time (eg, average and total amount)	11
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See note 6
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	16

the present article is based

Author notes

1. n/a, no missing data
2. n/a, no loss follow-up patient
3. n/a, not applicable
4. 6, figure 1
5. n/a, no missing data
6. n/a, not applicable