

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study in Taiwan
AUTHORS	Chan, Kun-Ming; Cheng, Chih-Hsien; Wu, Tsung-Han; Lee, Chen-Fang; Wu, Ting-Jung; Chou, Hong-Shiue; Lee, Wei-Chen

VERSION 1 – REVIEW

REVIEWER	Zhijun Zhu Beijing Friendship Hospital, Capital University, China
REVIEW RETURNED	12-Jun-2018

GENERAL COMMENTS	<p>This paper showed the outcome of patients who received liver grafts with the potential of bacterial infections. It is an interesting topic and the clinical data are valuable. However several confounding factors were not adjusted. Details of patient selection and grouping should also be cleared. The following issues should be clarified before it is accepted for publication.</p> <ol style="list-style-type: none">1. The criteria used to define the eligibility for organ donation should be explained. Were most of donors with infections screened out?2. How donor infection was decided by the “serial samples”? When an opportunistic pathogen was found only in urine without other positive findings, should the patient be referred to infection group?3. Were patients with potential fungal or other infections included? Which group were they referred to?4. Did the prophylaxis by antibiotics cover the bacteria found in donor samples?5. It is difficult to understand the meaning of the following statement: “This study was a retrospective observational study. Patients were not involved in this study.”6. The impact of antibacterial and antifungal prophylaxes should be analyzed.7. Discrepancies in baseline data should be adjusted by multivariate analysis.8. The causes of hospital mortality should be showed. Were bacterial infections account for the main reason of death?9. A language polishing need to be performed. Some expressions such as “we gathered our experience in deceased donor liver transplantation”, “the deceased donor shortage is very high particularly in Oriental countries” should be corrected.10. As reported in this article, acinetobacter baumannii found in one recipient was consistent with the culture result of the corresponding donor. Regarding most bacteria are sensitive to the antibacterial prophylaxes, antimicrobial resistance may have a
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	serious impact on donor derived bacterial infection. This should be discussed.
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REVIEWER	Vinay Sundaram Cedars-Sinai Medical Center, United States
REVIEW RETURNED	12-Jul-2018

GENERAL COMMENTS	<p>This is a good study, but I have the following suggestions.</p> <ol style="list-style-type: none"> 1. Please provide more information regarding the patient population, including a sample size calculation. please also include prevalence of diabetes in the two groups 2. Please provide a paragraph regarding additional discussion regarding antibiotic prophylaxis after transplant to prevent donor derived infections; they authors should discuss their current prophylaxis protocol and whther this provides adequate coverage for the bacterial infections cultured from donors 3. The primary outcome is survival. However, the study would benefit from a table regarding multiple outcomes including survival (number of deaths, not just survival analysis), but also bacterial infection in the peri-transplant period , acute cellular rejection, and sepsis.
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REVIEWER	Patrick Trottwe University of Cambridge, United Kingdom
REVIEW RETURNED	13-Jul-2018

GENERAL COMMENTS	<p>Paper title: Impact of donor with evidence of bacterial infections on deceased donor liver transplantation-A retrospective observational cohort study</p> <p>Overall comments to the Author This is an interesting study investigating the role that donor bacterial infections have on liver transplant recipient outcomes, with the overall aim of highlighting a group of deceased donors by which organ donation rates could be increased, in a country where this needs to occur. This retrospective study analysed the outcomes of 285 liver transplant recipients, of which 98 received a graft from a donor with a bacterial infection.</p> <p>The authors discuss the merits of this work eloquently in their discussion and introduction, particularly highlighting the differences noted in transplant practice worldwide and interpreting their results in this context. However, a concern is the papers wider applicability to transplant teams internationally, as it is common practice worldwide to use organs from donors with positive cultures. The concerns in doing this arise when the culture is associated with confirmed infection/sepsis in the donor or the infection is widely disseminated and may have caused damage to organs or tissues. The other concerns relate to antibiotic resistant organisms, which is a major public health concern and a particular concern in organ transplantation. Unfortunately this paper does not really address either of those concerns.</p> <p>In light of the above I have some questions that need addressed: 1. Were prophylactic antibiotics given to all recipients? If so what was the usual combination? Is it possible that transmission from donor to recipient occurred, but the organisms transmitted were susceptible to the antibiotics being given to the recipient, hence</p>
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	<p>there was never a clinical presentation of infection.</p> <p>2. The methods section states that cultures were usually taken. Is there a cohort in this study in which the donors did not have cultures taken?</p> <p>3. The coagulase negative staphylococcus in isolated in the donor blood cultures- were all of these thought to be true infection or are some the likely secondary to contamination.</p> <p>4. The authors should discuss their results in the context of different organ types. There is a body of literature suggesting, for example if you use lungs from a donor with a chest infection, the likelihood of bacterial transmission is high and the morbidity and mortality is also subsequently high.</p> <p>5. The authors should also discuss this policy in the context of multi-drug resistant bacteria. This is a growing concern internationally, and I wonder if the authors would still encourage use of organs from donors where the isolate identified in the donors was highly resistant.</p> <p>6. In the statistics section the authors should document the tests used to calculate the p-values when comparing their categorical and continuous data.</p> <p>7. I would suggest adding a number at risk table to the Kaplan-Meier to aide interpretation and for completeness.</p>
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VERSION 1 – AUTHOR RESPONSE

Reply to reviewer #1:

Comments:

This paper showed the outcome of patients who received liver grafts with the potential of bacterial infections. It is an interesting topic and the clinical data are valuable. However several confounding factors were not adjusted. Details of patient selection and grouping should also be cleared. The following issues should be clarified before it is accepted for publication.

1. The criteria used to define the eligibility for organ donation should be explained. Were most of donors with infections screened out?

Response

We appreciate the reviewer to give us a high value comment and interest in our manuscript. The eligible criteria of donor for organs donation and detail of infections screen were further clarified and described in the paragraph of “donor survey”. Briefly, all potential donor will be thoroughly checked by laboratory test, and several key examination to determine eligibility of organs donation or not. With regard to the assessment of bacterial infection, serial samples including bronchial aspirates, urine and blood were usually obtained for culture before organs donation. Donor had been hospitalization for long time, additional bacterial culture might be obtained if indicated in order to control infectious disease prior to organ 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.

Comments

2. How donor infection was decided by the “serial samples”? When an opportunistic pathogen was found only in urine without other positive findings, should the patient be referred to infection group?

Response

The author agree with reviewer’s comments that few opportunistic pathogens might have no harm to either donor or recipient. However, the study was designed to analyze patient’s outcome related to donor with evidence of bacterial infections. Therefore, any evidence of positive result from bacterial culture was categorized into the group of donor with bacterial infection.

Comments

3. Were patients with potential fungal or other infections included? Which group were they referred to?

Response

Donor-derived infectious diseases consist of viruses, bacteria, parasites and fungi, and all have the potential to be transmitted to the transplant recipient. 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 only focus on donor with bacterial infection and related impact immediately after liver transplantation. Therefore, fungus and other infections were not main issue to be analyzed in this study. This point had been further clarified in the “Introduction” section.

Comments

4. Did the prophylaxis by antibiotics cover the bacteria found in donor samples?

Response

The strategy of prophylactic antibiotics were described in the paragraph of “liver transplantation recipients”. 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. Additionally, antibiotic treatment specific to the recognized microorganisms from donor were also administered after transplantation based on the result of donor’s bacterial culture.

Comments

5. It is difficult to understand the meaning of the following statement: “This study was a retrospective observational study. Patients were not involved in this study.”

Response

This was based on the requirement of the Journal that need to include a statement of “Patient and public involvement statement”. The author had edited this part for easy to understand.

Comments

6. The impact of antibacterial and antifungal prophylaxes should be analyzed.

Response

Similar to response for previous comment, the study only focus on donor with bacterial infection and related impact immediately after liver transplantation. Therefore, fungus and other infections were not main issue to be analyzed in this study. Additionally, administration of antibacterial and antifungal regimens could be various based on the clinical situation of recipient’s infectious status. Therefore, it is hard to assess the impact of antibacterial and antifungal prophylaxes on recipient’s outcome as well as categorizing patients for analysis.

Comments

7. Discrepancies in baseline data should be adjusted by multivariate analysis.

Response

The author agree with reviewer’s opinion that a multivariate analysis might be better to show prognostic factor that affect recipient’s outcome. However, numerous factors could affect outcome of recipient after transplantation. As such, prognostic factors resulted from a multivariate analysis are largely influenced by clinical variables that included for analysis. A multivariate analysis perhaps would led to the study more complex. Hence, the study categorized patients into two groups based on donor with or without evidence of bacterial infections, and further clarified its clinical impact on deceased donor liver transplantation.

Comments

8. The causes of hospital mortality should be showed. Were bacterial infections account for the main reason of death?

Response

The causes of hospital mortality were shown in the Table 2. Severe bacterial infections accounted for most patient’s death in both groups. However, hospital mortality after LT were not significantly different between the two groups.

Comments

9. A language polishing need to be performed. Some expressions such as “we gathered our experience in deceased donor liver transplantation”, “the deceased donor shortage is very high particularly in Oriental countries” should be corrected.

Response

Actually, the manuscript had been edited by a native English speaker prior to submission. These sentences had been further corrected as reviewer’s request.

Comments

10. As reported in this article, *acinetobacter baumannii* found in one recipient was consistent with the culture result of the corresponding donor. Regarding most bacteria are sensitive to the antibacterial prophylaxes, antimicrobial resistance may have a serious impact on donor derived bacterial infection. This should be discussed.

Response

Issue related to antimicrobial resistance had been discussed in the “Discussion” section as follow. The possibility of potential donor with severe bacterial infections such as *Acinetobacter baumannii*, *vancomycin 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. 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.

Reply to reviewer #2:

Comments:

This is a good study, but I have the following suggestions.

1. Please provide more information regarding the patient population, including a sample size calculation. please also include prevalence of diabetes in the two groups.

Response

The author appreciate that the reviewer seconded this good study. Comorbidity of recipients at the time of transplantation were further shown in the Table 2. The prevalence of DM was higher in the Group I than that of Group II.

Comments:

2. Please provide a paragraph regarding additional discussion regarding antibiotic prophylaxis after transplant to prevent donor derived infections; they authors should discuss their current prophylaxis protocol and whether this provides adequate coverage for the bacterial infections cultured from donors.

Response

In the Methods section, the strategy of antibiotic prophylaxis was well described in the paragraph of "Liver transplantation recipients". Likewise, antibiotic prophylaxis was also well discussed in the last paragraph of Discussion section.

Comments

3. The primary outcome is survival. However, the study would benefit from a table regarding multiple outcomes including survival (number of deaths, not just survival analysis), but also bacterial infection in the peri-transplant period, acute cellular rejection, and sepsis.

Response

The outcomes of patients including current status and causes of mortality were summarized in the Table 2. The rates of hospital mortality within 30 days after LT was not significantly different between the two groups.

Reply to reviewer #3:

Comments:

This is an interesting study investigating the role that donor bacterial infections have on liver transplant recipient outcomes, with the overall aim of highlighting a group of deceased donors by which organ donation rates could be increased, in a country where this needs to occur. This retrospective study analysed the outcomes of 285 liver transplant recipients, of which 98 received a graft from a donor with a bacterial infection.

The authors discuss the merits of this work eloquently in their discussion and introduction, particularly highlighting the differences noted in transplant practice worldwide and interpreting their results in this context. However, a concern is the papers wider applicability to transplant teams internationally, as it is common practice worldwide to use organs from donors with positive cultures. The concerns in doing this arise when the culture is associated with confirmed infection/sepsis in the donor or the infection is widely disseminated and may have caused damage to organs or tissues. The other concerns relate to antibiotic resistant organisms, which is a major public health concern and a particular concern in organ transplantation. Unfortunately this paper does not really address either of those concerns.

In light of the above I have some questions that need addressed:

1. Were prophylactic antibiotics given to all recipients? If so what was the usual combination? Is it possible that transmission from donor to recipient occurred, but the organisms transmitted were susceptible to the antibiotics being given to the recipient, hence there was never a clinical presentation of infection.

Response

The author thank the reviewer for his valuable comments and suggestions. Both concerned issues by the reviewer were further discussed in the manuscript now, and the author wish the revision could answer the reviewer's questions and meet the requirement of considering acceptable for publication in the journal. The preventive strategy of antibiotic prophylaxis was administered for all recipients, and was mainly rely on the clinical status of the recipient. In the Methods section, the strategy of antibiotic prophylaxis was well described in the paragraph of "Liver transplantation recipients". Likewise, antibiotic prophylaxis was also well discussed in the last paragraph of Discussion section.

Comments

2. The methods section states that cultures were usually taken. Is there a cohort in this study in which the donors did not have cultures taken?

Response

All potential donor will be thoroughly checked by laboratory test, and several key examination to determine eligibility of organs donation or not. With regard to the assessment of bacterial infection, serial samples including bronchial aspirates, urine and blood were usually obtained for culture before organs donation. Donor had been hospitalization for long time, additional bacterial culture might be obtained if indicated in order to control infectious disease prior to organ donation. Therefore, all donors had cultures taken.

Comments

3. The coagulase negative staphylococcus in isolated in the donor blood cultures were all of these thought to be true infection or are some the likely secondary to contamination.

Response

Indeed, few results from cultures might be related to either translocation from the gastrointestinal tract or contamination. As the statement in the Discussion, few pathogens cultured from donors could be ignored, and the donors should not be excluded from organ donation. However, the study aimed to analyze the impact of donor with evidence of bacterial infection. Therefore, the study categorized all patients who received a liver graft from donor with positive bacterial culture in the Group I for analysis.

Comments

4. The authors should discuss their results in the context of different organ types. There is a body of literature suggesting, for example if you use lungs from a donor with a chest infection, the likelihood of bacterial transmission is high and the morbidity and mortality is also subsequently high.

Response

The author agree with the reviewer's opinion that the impact of donor infections could be difference in different type of organs transplantation. Ideally, it would be better to discuss the impact of donor infections in all types of transplantation. However, other organ transplantations are far beyond my expertise and capability. Honestly, it might be not appropriate for the author to discuss and comment on other types of transplantation based on our limited knowledge.

Comments

5. The authors should also discuss this policy in the context of multi-drug resistant bacteria. This is a growing concern internationally, and I wonder if the authors would still encourage use of organs from donors where the isolate identified in the donors was highly resistant.

Response

With regard to the issue, the author had further discussed in the Discussion section. Indeed, the possibility of potential donor with multi-drug resistant bacteria might be existed. 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. 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.

Comments

6. In the statistics section the authors should document the tests used to calculate the *p*-values when comparing their categorical and continuous data.

Response

The tests used to calculate the *p*-values when comparing categorical and continuous data were further described in the statistic section.

Comments

7. I would suggest adding a number at risk table to the Kaplan-Meier to aide interpretation and for completeness.

Response

Number at risk had been included in the survival figure.

VERSION 2 – REVIEW

REVIEWER	Zhijun Zhu Liver Transplantation Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China.
REVIEW RETURNED	10-Aug-2018

GENERAL COMMENTS	<p>1 The sensitivity and specificity of bacterial culture were low. Other measurement or criteria for infection should be employed.</p> <p>2 Confounding factors should be analyzed and discussed.</p> <p>3 Low incidences of infection, insufficient sample size and low accuracy of detection method may result in a negative finding. The result of this study should not be over interpreted.</p>
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REVIEWER	Patrick Trotter University of Cambridge, United Kingdom
REVIEW RETURNED	06-Sep-2018

GENERAL COMMENTS	<p>Overall comments to the Author</p> <p>The authors have discuss the merits of this work eloquently in their discussion and introduction. They have also addressed many of my prior comments.</p> <p>However, I still have concerns to the papers wider applicability to transplant teams internationally, as it is common practice worldwide to use organs from donors with positive cultures.</p> <p>I also feel the paper would benefit from general grammatical improvements.</p> <p>I also feel that in order to fully draw conclusions from their survival analysis performing a cox hazards regression analysis would be useful. This would allow the authors to draw firmer conclusion</p>
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VERSION 2 – AUTHOR RESPONSE

Reply to reviewer #1:

Comments:

1 The sensitivity and specificity of bacterial culture were low. Other measurement or criteria for infection should be employed.

2 Confounding factors should be analyzed and discussed.

3 Low incidences of infection, insufficient sample size and low accuracy of detection method may result in a negative finding. The result of this study should not be over interpreted.

Response

1. The authors agree with the reviewer's opinion regarding low sensitivity and specificity of bacterial culture. However, the only strong evidence of bacterial infection in clinical scenario is still rely on culture. Other parameters such as leukocytosis, elevation of neutrophil as well as C-reactive protein et al. are more nonspecific for definition of bacterial infection. Therefore, the study emphasize on the evidence of bacterial infection based on the bacterial culture as shown in the manuscript's title and described in the introduction.
2. In order to minimize the influence of confounding factors on the result, a propensity score matching of survival analysis was performed. The comparison of overall survival between the two groups after a propensity score matching was not significant difference.
3. The authors appreciate the reviewer's concern that the study should cautiously interpret the result. Nowadays, a bacterial infection in the donor is generally acceptable for organ donation due to scarcity of organ donation worldwide. As the statement in the conclusion section, the study is limited by its retrospective entity in a single transplantation center with a small number of patients. The study is merely to imply that donor with bacterial infection should not totally preclude the use of organs donation for transplantation.

Reply to reviewer #3:

Comments:

The authors have discuss the merits of this work eloquently in their discussion and introduction. They have also addressed many of my prior comments.

However, I still have concerns to the papers wider applicability to transplant teams internationally, as it is common practice worldwide to use organs from donors with positive cultures.

I also feel the paper would benefit from general grammatical improvements.

I also feel that in order to fully draw conclusions from their survival analysis performing a cox hazards regression analysis would be useful. This would allow the authors to draw firmer conclusions.

Response

1. The authors thank the reviewer for his valuable comments and suggestions. Indeed, it is common practice worldwide to use organs from donors with positive cultures. The limitation of the study was well stated in the conclusion section. Additionally, the study pointed several marked observation that might be helpful in clinical practice.
2. Actually, the manuscript had been edited by an English editing company prior to submission, and the author had tried the best to improve the English writing.
3. Finally, a multivariate analysis of variable was performed using a cox hazards regression analysis as shown in supplemental table 1. The result confirmed that bacterial infection in donor was not a significant prognostic factor of patient's outcome after liver transplantation.

VERSION 3 – REVIEW

REVIEWER	Zhi-Jun Zhu Liver Transplantation Center, Clinical Center for Pediatric Liver Transplantation, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University Beijing 100050, China
REVIEW RETURNED	13-Dec-2018

GENERAL COMMENTS	This article has focused on the important clinical question about the relationship between donors' infection and recipients' prognosis, although statistics and design are not sufficient to fully draw a very clear conclusion, this work was meaningful. I have fully expressed the comments and opinions on this article before. Based on the actual clinical situation, I don't think it is necessary to make further modifications. And it can be considered for acceptance.
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REVIEWER	Patrick Trotter University of Cambridge, United Kingdom
REVIEW RETURNED	28-Oct-2018

GENERAL COMMENTS	The authors have addressed the concerns I had with their manuscript. I still have concerns regarding the wider applicability of this study, but appreciate that the authors have made attempts to address this limitation in their discussion.
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