Risk factors of graft failure are well described. Study population - Kidney graft failure (return to dialysis or death with a functioning graft) is usually preceded by an increase of serum creatinine.

Hypothesis: Some factors are correlated with

- serum creatinine increase, leading to graft loss
- graft failure without changes of serum creatinine in the follow-up
- both serum creatinine changes in the follow-up and graft failure risk, independently of serum creatinine evolution

OBJECTIVE

To investigate the etiological role of recipient, donor and transplant characteristics on creatinine changes within the follow-up and/or graft failure risk.

MATERIALS AND METHODS

Study population - Transplanted patients were selected from the French prospective DIVAT cohort (www.divat.fr) as follows:

- Adult recipients from living or heart beating deceased donors
- Transplanted for the first or second time between 2000 and 2013
- Maintained under Tacrolimus and MMF
- Alive with a functioning graft at 1-year post transplantation

Kidney transplantation outcomes

- Longitudinal process: serum creatinine (µmol/L) measurements yearly recorded until the graft failure.
- Survival process: graft failure (first event between return to dialysis and death with a functioning graft).

Statistical analyses - We proposed a joint model for longitudinal and time-to-event data (Rizopoulos 2012) allowing correctly modelize each process, quantify their relationship and avoid the possible bias observed when Cox model or mixed model are used separately (Asar 2015).

RESULTS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Association with serum creatinine at 1-year</th>
<th>Graft failure risk</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>recipient men</td>
<td>0</td>
<td>0</td>
<td>1674 (60.30)</td>
<td>0</td>
</tr>
<tr>
<td>Recipient</td>
<td>female</td>
<td>0</td>
<td>0</td>
<td>1674 (60.30)</td>
</tr>
</tbody>
</table>

Follow-up description

Return to dialysis: 278; death with a functioning graft: 205

12843 measurements of serum creatinine (median of 4 values/patient).

Results of the joint model

Level of serum creatinine (µmol/L, for 25% higher)

Recipient gender (male vs female) 7 -0.0001 7 <0.0001
Donor age (for 10 years higher) 4 -0.0001 4 <0.0001
Serum creatinine at 3 months (for 50 µmol/L higher) 7 -0.0001 7 <0.0001
History of diabetes (yes vs no) 0 0.0000 15 <0.0001
Cold ischemia time (for 10 h higher) 0 0.0267
Serum creatinine at 6 months (for 50 µmol/L higher) 16 -0.0001 16 <0.0001 0.78 <0.0001
Recipient age (for 10 years older) 4 -0.0001 4 <0.0001
Immunisation anti-HLA class I (+ vs -) 2 -0.0001 -5 <0.0001 1.35 <0.0001
Histocompatibility mismatch (ABDR > 4) 7 -0.0001 7 <0.0001
Acute rejection episode < 1 year (yes vs no) 6 -0.0001 -5 0.0048 1.43 <0.0001
History of cardiovascular diseases (yes vs no) 0 0.0000 15 <0.0001
Graft rank (second vs first) 0 0.0000 0 0.0118

INTERPRETATION

- Direct associations with graft failure risk are identified in red.
  - For instance, patients with history of cardiovascular disease have the same level of serum creatinine during the follow up but they are at higher risk of graft failure compared to patients without cardiovascular history (HR=1.37).
  - Some variables are associated independently with both the serum creatinine changes and the graft failure risk (in blue).
    - Ex: Immunized patients have a serum creatinine 7% higher compared to non immunized patients after 5 years. However, after adjustment on serum creatinine changes, immunized patients are still at higher risk of graft failure compared to non immunized patients (HR=1.46).

CONCLUSION

- This suitable model enhances the clinical message respecting methodological concepts.
  - The whole serum creatinine trajectory is considered.
  - Graft failure risk is adjusted on serum creatinine change.
  - Serum creatinine changes and graft failure risk relationship is quantified.

- Biological knowledge allows causality ⇒ etiological role

- Physicians should pay a particular attention such to elderly or immunized recipients, second transplant, patients with history of cardiovascular disease, those for which an acute rejection was occurred. For these patients, the isolated monitoring of serum creatinine (adjusted) did not appear useful to evaluate the risk of graft failure.

REFERENCES


The authors declare no competing financial interests.