

# Predicting post-surgery outcome after kidney transplantation by a comorbidity index

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## Abstract

**Background and aim:** An easily accessible pre-transplant tool to better predict post-surgery outcome following kidney transplantation in elderly recipients is warranted. We investigated whether the Liu Comorbidity Index (LCI) may predict early admission to Intensive Care Unit (ICU) and post-operative mortality in kidney recipients  $\geq 55$  years of age.

**Patients and methods:** Data from all patients  $\geq 55$  years who underwent kidney transplantation at our center from 2011–2015 were included. LCI consists of 11 comorbidity covariates creating a 21 point scale. A pre-transplant LCI was registered as the sum of the weights corresponding to the individual conditions present. Post-transplant survival data and ICU admission data were extracted from hospital records and from the Norwegian Renal Registry.

**Results:** 639 recipients  $\geq 55$  years (mean age  $66.0 \pm 6.5$ ) were analysed and their mean LCI score was  $2.6 (\pm 2.4)$ . 98 recipients (15%) were admitted to the ICU during the early post-operative phase, and thirty-seven stayed more than 24hr. A LCI score  $\geq 7$  ( $p=0.002$ ) and ICU stay  $\geq 24$  ( $p \leq 0.001$ ) hours were both independently associated with impaired patient survival. An elevated LCI score was associated with increased risk of admittance to the ICU ( $p=0.001$ )

**Conclusion:** An elevated pre-transplant LCI score was associated with increased risk of ICU admission and impaired survival post kidney-transplantation in middle-aged and elderly recipients.

## Introduction

Successful kidney transplantation (KTx) is the optimal treatment for patients with end-stage renal disease (ESRD) regardless of age [1–3]. KTx is considered a safe surgical intervention. Despite increased patient and graft survival caused by improvements in the perioperative management and new immunosuppression protocols, the number of kidney transplant recipients (KTR) in need of intensive care treatment after engraftment seems to increase [4]. An increasing number of elderly recipients, often with several comorbidities might explain this tendency [5]. It has been reported that life-threatening complications warranting ICU admission occur in about 5% to 10% of the kidney transplant recipients with the early post-operative phase being the most critical time-period [6]. An improved preoperative selection to limit the risk of an adverse postoperative outcome is warranted. The Charlson Comorbidity Index (CCI) was developed in 1987 for mortality analysis based on patients without renal failure admitted for medical services [7], and has often been used for assessment of comorbidities, including in kidney transplant recipients [8]. However, it still remains uncertain if the CCI conditions actually can describe the comorbidity burden for ESRD patients [9] in the 20<sup>th</sup> century. In a previous study in KTR older than 70 years we showed that a pre-operative CCI was not associated with post-transplant survival rates [10]. In line with this, McArthur, *et al.* recently published a large retrospective cohort study including data from 4111 Canadian kidney transplant recipients and concluded that existing comorbidity indices could not predict 1-year mortality

in patients with chronic kidney disease [11]. Unfortunately, they did not evaluate the comorbidity index published by Liu, *et al* [9]. This index predicts survival based on a cohort from the US renal registry examining the comorbid conditions among dialysis patients. At our center we have included the Liu Comorbidity Index (LCI) as part of our routine pre-transplant work-up since 2012.

In this single center study, we explored if a pre-operative LCI score can predict post-engraftment ICU admission and survival in a cohort of KTR aging 55 years and older.

## Materials and methods

All KTR age  $\geq 55$  year who received a kidney graft at the national transplant center between January 1<sup>st</sup>, 2011 and December 31<sup>st</sup> 2015 were included in this single center retrospective cohort study.

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The pre-transplant evaluation and preoperative work-up of KTR is standardized and follows current guidelines. Cardiovascular evaluation includes a regular electrocardiography (ECG) and echocardiography (ECHO) with a physical evaluation and examination by a cardiologist. If there is a history of previous CV-disease or doubt a stress ECG/ECHO or coronary angiogram is performed prior to enlisting [12]. All transplantations were performed with uniform anaesthesia, perioperative care and surgical technique and the patients received a standardized immunosuppressive regimen [13].

Comorbidity was routinely assessed as part of the pre-transplant medical work-up and LCI was calculated as the sum of the weights corresponding to the individual conditions present (Table 1). As described by Liu in the original publication the recipients were divided into low (0-3), moderate (4-6) and elevated ( $\geq 7$ ) LCI risk score [9]. The LCI was not used to assess patients eligible for transplant listing. The study was performed in accordance with the Declaration of Helsinki 2000. The clinical and research activities are consistent with the principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism". All patients gave written consent. Out-come data were retrieved from the electronic patient records and from the Norwegian Renal Registry.

At our center KTR are routinely transferred directly from the operating room (OR) to a High Dependency Unit (HDU) at the surgical ward. Patients not extubated in the OR and patients considered to be at high risk for developing (in particular) cardiopulmonary postoperative complications are transferred to the ICU (critical care level 3) directly from the OR. Patients developing postoperative complications at the surgical ward are, when indicated, transferred to the ICU for advanced monitoring and support. The most serious medical problem leading to ICU admission was registered in the study as the main ICU admission reason.

Due to the fact that there is only one transplant center and the long distances in Norway all KTR normally receives post-transplantation follow-up at an out-patients clinic at our center for approximately 8 weeks. This gives complete data for all patients from the early post-engraftment period including need of hospitalizing and medical care. After 8 weeks the patients are transferred to their local nephrology center.

## Statistics

Survival was analyzed using Kaplan-Meier and Cox regression models. Associations between LCI score and ICU admission were analyzed in multivariate logistic regression models. We used chi-squared or Fishers exact test for categorical variables and unpaired

t-tests for continuous variables. All reported p-values were two-sided and probability levels below 0.05 were considered significant. All statistical analyses were performed using the IBM SPSS statistics version 24.

## Results

A total of 1398 kidney transplantations were performed during the study period. Six hundred and thirty-nine (46%) recipients were 55 years or older (mean age  $\pm$  SD;  $66.0 \pm 6.5$ ) and were included in the final analyses. Four hundred and forty-seven (70%) were male. Overall mean LCI score was  $2.6 (\pm 2.4)$ . Ninety-eight recipients (15% of the study population) were admitted to the ICU during the early post-operative phase and 37 (8%) stayed for more than 24 hr. Cardio-respiratory failure was the main reason for ICU admission (54%). Baseline characteristics are presented in Table 2. The proportion of elderly, time on waiting list and dialysis vintage seems to be higher in the group of recipients staying  $>24$ h in ICU. There was no ICU mortality. The median LCI score was 2 in the non-ICU group (range 0-13), 3 in the ICU  $<24$  hr (range 0-8) ( $p=0.001$  vs. non-ICU), and 4 in the ICU  $>24$  hr (range 0-12) ( $p<0.001$  vs. non-ICU). LCI score  $\geq 7$  and ICU stay  $\geq 24$  hours were both independently associated with impaired survival (Figures 1 and 2, Table 3). An elevated pre-transplant LCI score was associated with and increased risk of admittance to ICU (Table 4).

## Discussion

Our data revealed that elderly recipients with a pre-transplant LCI score  $> 7$  had more than twice the risk of significantly impaired post-engraftment survival compared to recipients with LCI  $<3$ . It is indeed noteworthy that even in our selected cohort of transplant candidates with presumably low comorbidity the LCI seems to be strongly associated with post engraftment survival. This finding may be helpful in the pre-transplant clinical evaluation of middle-aged and elderly kidney transplant candidates indicating that this is a "patients at risk" in need of special perioperative attention and early post-engraftment care.

As a result of the aging population, an increased number of older patients develop ESRD and become potential KTx candidates. This leads to an increasing demand of the transplant program and even though kidney transplantation is considered as a safe and recommended treatment for most patients with ESRD including older patients [14], some patients will be "too sick to transplant". The KTx waiting time is currently short in our center (overall median approximately 15-18 months for first KTx) in contrast to many other centers that often have an average wait list of 3-5 years [15]. In addition, younger recipients will often be given priority over older resulting in even longer waiting times for older KTR candidates. At present, the decision about which patients are suitable for KTx is generally performed based on the standardized medical work-up combined with a clinical judgment. A publication by Kan, *et al.* evaluated the LCI in a very large, elderly ( $\geq 65$  years of age) dialysis population and finds it to be a strong predictor of survival [16]. This gives support to our findings indicating that in the elderly, often high-risk candidates, the LCI could provide valuable additional information in the preoperative assessment and risk stratification.

There are several ways to assess comorbidity. In a recent study comparing five comorbidity indices McArthur, *et al.* conclude that none of the evaluated indices were able to accurately predict one-year mortality in CKD patients [11]. The CCI has previously been validated as a useful tool in adult and middle aged KTR. However, in studies of patients older than 70 years, comorbidity determined by CCI has

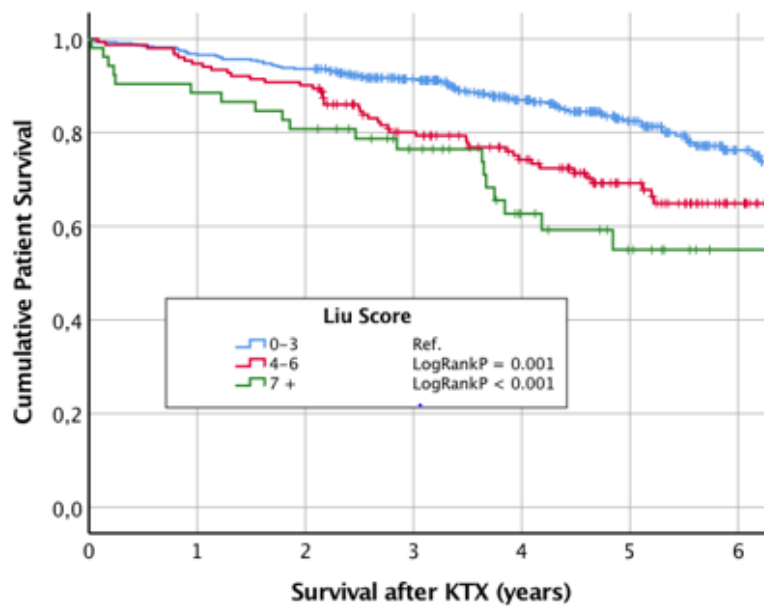
**Table 1.** Liu Comorbidity Index

| Liu Comorbidity Index                 |       |
|---------------------------------------|-------|
| Comorbid conditions                   | Score |
| Diabetes mellitus                     | 1     |
| Congestive heart failure              | 3     |
| Coronary artery disease               | 1     |
| Cerebrovascular disease               | 2     |
| Peripheral vascular disease           | 2     |
| Other cardiac                         | 2     |
| Dysrhythmia                           | 2     |
| Chronic obstructive pulmonary disease | 2     |
| Gastrointestinal bleeding             | 2     |
| Liver disease                         | 2     |
| Cancer                                | 2     |

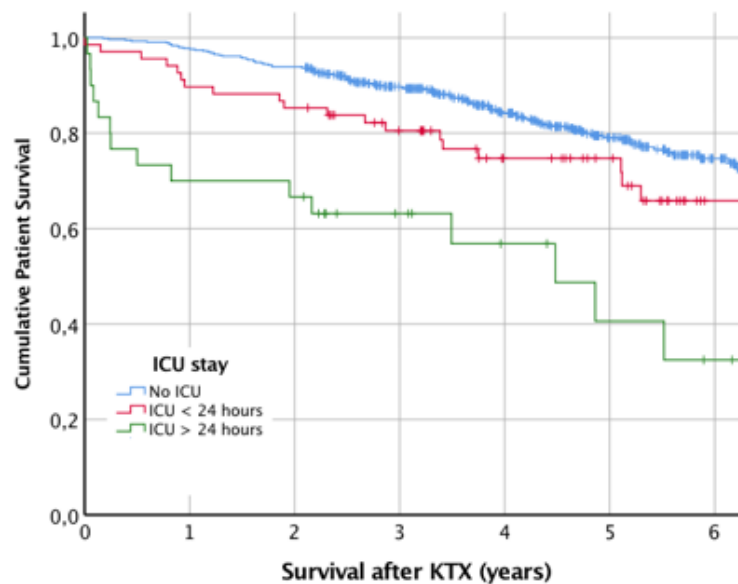
**Table 2.** Baseline characteristics

| Variables                                     | All recipients (n=639) | Admitted ICU (n=98) | ICU > 24h (n=37) |
|---|------------------------|---------------------|------------------|
| Age (mean age ± SD)                           | 66.0 ± 6.6             | 66.5 ± 6.4          | 67.3 ± 6.9       |
| Gender (m/f)                                  | 448/191                | 66/32               | 23/14            |
| First KTx, n (%)                              | 620 (97)               | 89 (91)             | 31 (84)          |
| Previous KTx, n (%)                           | 19 (3)                 | 9 (9)               | 6 (16)           |
| Pre-emptive KTx, n (%)                        | 166 (26)               | 28 (29)             | 7 (19)           |
| LD / DD                                       | 118/521                | 13/85               | 4/33             |
| Time in dialysis (months) (median, range)     | 21 (1-108)             | 27 (3-108)          | 31 (3-108)       |
| Time on waiting list (months) (median, range) | 12 (0.1-104)           | 13 (0.3-108)        | 15 (0.3-104)     |
| LCI 0-3, n (%)                                | 437 (68)               | 51 (52)             | 17 (46)          |
| LCI 4-6, n (%)                                | 150 (24)               | 32 (33)             | 13 (35)          |
| LCI ≥ 7, n (%)                                | 52 (8)                 | 15 (15)             | 7 (19)           |

KTx: Kidney Transplantation; LD: Living donor; DD: Deceased donor; LCI: Liu Comorbidity Index; ICU: Intensive care unit



**Figure 1.** Patient survival according to Liu Comorbidity score



**Figure 2.** Patient survival according to ICU stay within the first 40 post-operative days

**Table 3.** Multivariable Cox regression model adjusted for age and gender, describing associations between Liu comorbidity score, ICU admission and patient death

| Multivariable Cox regression model | HR (95% CI)      | P-value |
|------------------------------------|------------------|---------|
| LCI score 0-3                      | Reference        |         |
| LCI score 4-6 vs. 0-3              | 1.46 (0.99-2.14) | 0.055   |
| LCI score ≥ 7 vs. 0-3              | 2.27 (1.36-3.77) | 0.002   |
| No ICU                             | Reference        |         |
| ICU < 24 hours vs. no ICU          | 1.43 (0.87-2.35) | 0.154   |
| ICU > 24 hours vs. no ICU          | 3.72 (2.15-6.45) | <0.001  |
| Age (per year)                     | 1.06 (1.03-1.09) | <0.001  |
| Male Gender                        | 1.06 (0.72-1.56) | 0.760   |

**Table 4.** Logistic regression model analyses adjusted for age and gender, describing associations between Liu comorbidity score and ICU admission

| ICU admission | N   | OR (95% CI)       | P-value   |
|---------------|-----|-------------------|-----------|
| LCI score 0-3 | 436 | Reference         | Reference |
| LCI score 4-6 | 151 | 2.18 (1.33-3.58)  | 0.002     |
| LCI score ≥ 7 | 52  | 3.24 (1.64-6.38)  | 0.001     |
| Age           | 639 | 1.01 (0.98-1.04)  | 0.625     |
| Male Gender   | 639 | 0.75 (0.47-1.21)  | 0.241     |
| ICU >24 hours |     |                   |           |
| LCI score 0-3 | 436 | Reference         | Reference |
| LCI score 4-6 | 151 | 2.20 (0.93-5.23)  | 0.073     |
| LCI score ≥ 7 | 52  | 5.08 (1.89-13.66) | 0.001     |
| Age           | 639 | 1.03 (0.98-1.10)  | 0.259     |
| Male Gender   | 639 | 0.70 (0.31-1.56)  | 0.380     |

not been associated with increased mortality [10,17]. The Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score published by Laging, *et al.* was developed based on data from KTR [18]. However, when the authors compared comorbidity assessed by the RoCKeT score and CCI, they demonstrated that even if a high comorbidity score was associated with a low post transplant survival, the only single diagnose that was significantly negatively associated with survival was the presence of pre-transplant peripheral vascular disease (PVD). They concluded that despite severe comorbidity, these patients had good post-transplant survival and should consequently be considered for kidney transplantation. It should be noted that the mean age in the study by Laging, *et al.* was 56.3 years compared to 66 years in our study.

Because of limited remaining life span, the absolute survival benefit of transplantation over dialysis in older patients is much smaller than in younger patients [1,19,20]. McArthur, *et al.* called for a comorbidity index that was specifically developed for CKD patients [11]. They did however not include the LCI score or the RoCKeT score in their evaluation. None of the available comorbidity indices were primarily developed to decide whether a patient with ESRD should be enlisted or not, but our findings indicate that the LCI score may be useful as an additional tool in the evaluation process of older kidney transplant candidates.

An elevated LCI score did not only indicate impaired survival, but also increased risk of ICU admission, which in turn implies significantly prolonged hospitalization and direct post-engraftment treatment associated costs. However, a successful KTR will in relatively short time outweigh the cost of continuous dialysis [21]. Patients with low functional capacity have higher mortality rate after KTx than candidates with higher functional capacity, however even in patients with the lowest functional status a better long-term survival is anticipated with a functioning kidney transplant vs. continuous dialysis [22,23]. It should also be noted that even older KTR experience improved health related quality of life after transplantation [24]. The decision to accept a patient

for kidney transplantation should consequently be performed based on expected quality of life, expected life span and treatment related costs with and without transplantation.

Our study has several strengths and limitations. The data analyzed are from a single national center and includes all KTR older than 55 years receiving a transplant in the study period. It is consequently representative for the Norwegian KTR population and our current transplant protocol. Generalization to other transplant centers may be difficult due to differences in selection of older KTR candidates, waiting times, ethnicity and possibly referral policies. However, knowing that the ethnicity within Scandinavia/northern Europe is quite similar and the fact that many centers also accept older recipients makes it likely that the findings would be valid in these centers as well. The registration of comorbidity data was performed prospectively as a part of regular transplantation work-up, but since the registration are performed by nephrologists from 25 nephrology centers, a uniform registration of comorbidities cannot be guaranteed. Even though all data used in this study were registered prospectively, the collection of data was performed in retrospect.

### Conclusion

In conclusion, an elevated pre-transplant LCI score predict impaired survival and increased admission rate to intensive care post-engraftment in older and middle-aged kidney transplant recipients. These findings indicate that a pre-transplant LCI may become a useful additional tool in the evaluation of older kidney transplant candidates in need of individualized postoperative follow-up.

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