The use of screening computed tomography prior to renal transplantation should be limited to high-risk patients with advanced age, coronary artery disease and diabetes mellitus

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ABSTRACT

Background: Computed tomography (CT) scans’ predictive value is not well established for screening prior to renal transplantation. The purpose of this study is to measure the extent to which CT findings during transplant evaluation alter candidacy.

Methods: Data for 639 renal transplant candidates who underwent CT screening were obtained. Of these, 454 patients had sufficient data and met criterium of having undergone screening CT within six months of official renal transplant evaluation. Transplant status before and after CT imaging was assessed.

Results: Those who had screening CTs prior to renal transplantation who were older (p=0.01), had coronary artery disease (p=0.006), or had diabetes mellitus (p=0.042) had significant waitlist status changes. Candidates whose CT findings included vascular calcification or pulmonary nodules were more likely to be permanently excluded from the waitlist (p<0.05). Thirty-two, or 7.0%, had a permanent waitlist status change due to pathologic CT findings that precluded transplantation.

Conclusions: Focusing on older patients with coronary artery disease, atherosclerosis, or diabetes would reduce the number of CTs obtained during workup. Candidates with systemic vascular calcification or pulmonary nodules found on subsequent imaging are at the greatest risk for permanent exclusion from renal transplantation.

Keywords: Diagnostic techniques and imaging, Computed tomography, Kidney transplantation, Living donor, Waitlist management, Registry analysis

INTRODUCTION

The growing global incidence of chronic kidney disease (CKD) overwhelms the healthcare system.1 The absolute number of people with end stage renal disease (ESRD) continues to increase due to diabetes and the aging population.2,3 In 2014, there were over 118,000 new cases of ESRD in the United States, an increase of nearly 2%.4 Of these, 44% of were associated with a history of diabetes, the most common etiology.

In those with ESRD, kidney transplantation offers a lower overall cost of care and higher quality of life compared to hemodialysis.5,6 Yearly expenditures associated with the care of patients on dialysis are three times that of transplant patients.5,7 Patients older than 70 have an expected survival of 4.5 years on the renal...
transplant waiting list compared to 8.2 years with transplantation.8 

Individuals with ESRD must be comprehensively evaluated prior to renal transplant surgery. Harmath et al suggested that imaging was an universal requirement of transplant evaluation, yet its use as a screening tool was not advocated in universal imaging protocols for transplantation.9 It is widely believed that computed tomography (CT) provides preoperative knowledge of the transplant candidate’s anatomy, targets for anastomosis, vascular abnormalities, atherosclerotic disease, malignancy, lung nodules, and other issues that would preclude renal transplantation.9

With comprehensive CT imaging suggested or performed for all transplant candidates, increasing medical expense becomes a critical area of consideration.10 Despite growing attention on healthcare spending in the United States, health costs account for a larger percentage of the gross domestic product (GDP) than any other developed country.11 In 2010, medical costs equalled 16% of the country’s GDP, and increased to 18% in 2015.12 The Centers for Medicare and Medicaid Services estimates that by 2025, it will comprise 20% of the national GDP.13 ESRD alone accounted for $28.6 billion of healthcare spending and over 5% of total Medicare payments for the year of 2012.7 The use rate of computed tomography (CT) increased from 361 per 1000 beneficiaries in 2001 to 514 per 1000 beneficiaries in 2014.14 It is estimated that advanced imaging accounted for over $100 billion, or 10%, of total healthcare spending in 2006.15 Moreover, Brenner et al. suggest that 20-50% of all diagnostic imaging is inappropriate or fails to provide further information to improve patient outcomes.16 Unnecessary imaging also increases concerns about radiation safety in patients, especially those with multiple comorbidities. It is estimated that half of all radiation exposure in the general population is due to medical imaging alone.16 Annual allowable occupational radiation exposure in Europe is rated at 20 mSv, while in the United States the acceptable level of exposure is 50 mSv.17,18 Even minimal radiation exposure poses health risks. Approximately 16.5% of all patients receiving medical imaging in 2010 received a single CT.19 Per the National Academy of Sciences’ National Research Council, the dose of radiation from just one CT (10 mSv) may increase risk of future malignancy.20 CT protocols should consider this additional risk, cost and burden during transplant evaluations.

Medical providers help evaluate and refine healthcare protocols to reduce costs and increase safety by eliminating procedures and interventions that add little patient care benefit.21 In renal transplantation evaluations, expenses can be reduced by eliminating transplant evaluation CTs in situations where the imaging does not add significant value. Via a detailed medical history, patients at higher risk of an abnormal finding which would complicate or preclude transplantation can be readily identified to determine who benefits from the imaging. The predictive value of the CT scans is not well established for screening prior to renal transplantation. The purpose is to measure the extent to which CT findings during transplant evaluation change the outcome of candidacy and to determine which populations benefit from a renal transplant evaluation CT.

**METHODS**

**Data acquisition**

A retrospective review of 639 renal transplantation candidates at University of Toledo Medical Center (UTMC) was performed using the established database Transchart, as approved by IRB. The database consolidates candidates’ hospital records, inclusive of but not limited to demographics, past medical and surgical history, relevant laboratory testing and imaging during transplantation candidacy, and transplant history and waitlist status throughout workup. Records of renal transplant candidates from 2009 to 2015 were obtained. At this institution, all adult transplant candidates are screened using a non-contrast CT of the abdomen and pelvis. Candidates without corresponding CT studies during the transplantation process were filtered. To account for changes in variables that could occur during an extended wait time between a CT and the official transplant evaluation, only renal transplant candidates with CT imaging within six months of evaluation were included. Demographic information including race, gender, and age were obtained. Ethnicity was identified as Caucasian, African American, Hispanic, or “other”, while gender was identified as male or female. Past medical history, including body mass index (BMI) and history of hypertension, dialysis, coronary artery disease, malignancy, congestive heart failure, diabetes, prior renal transplantation, smoking status, and blood type was also reviewed.

**Outcome measures**

The data for candidates who received non-indicated CTs was compiled (Figure 1). A non-indicated CT was defined as CT imaging obtained within six months of the renal transplant evaluation date for screening purposes only. Indicated CT studies were defined as imaging performed to investigate underlying conditions or suspicious findings and not merely for a screening evaluation. Prior to analysis, indicated CTs were filtered. The findings from the imaging were listed as separate data points based on type (Figure 2) including vascular calcifications, renal masses, pulmonary nodules, intraductal papillary mucinous neoplasms (IPMN) of the pancreas, and malignancies. If further investigation was performed due to these findings, this was noted. The transplant status of each patient was then identified and analyzed to determine whether any of the findings from the non-indicated imaging studies, or subsequent diagnostic workup, resulted in candidate exclusion from
renal transplantation. It is important to note that focal and mild vascular calcifications did not exclude patients from transplantation; only those with either moderate to severe or diffuse calcifications were removed. In cases of multiple comorbidities, only factors that ultimately lead to candidacy exclusion categorized patients. In general, the findings of the CT imaging were not used as the single determining factor for renal transplant candidacy, but more so as a tool to help determine the possibility of undergoing a successful renal transplant in those deemed to be not ideal candidates. Candidacy for renal transplantation and demographic information were examined for any correlation. During analysis, ineligible candidates due to either CT findings or medical comorbidities were listed as a change in renal transplant waitlist status.

Figure 1: Flowchart detailing the methodology for patient and characteristic selection.

Figure 2: Flowchart detailing how outcome measures were determined.
Statistical analysis

Those with indicated CTs or no CTs were removed from the final analysis. Continuous variables, such as age and BMI, were kept unmodified and analyzed with either the Mann-Whitney U test or Kruskal-Wallis test. All categorical variables were modified to a binary system where “0” denoted a negative finding and “1” denoted a positive finding. Median values for continuous variables were used during comparison. All other variables in the data set were determined to be categorical and analyzed using Pearson’s chi-squared test. A p value of 0.05 was the cutoff for significance for both continuous and categorical variables. All statistical analysis was conducted using SPSS Statistics software (IBM, 23.0, Armonk, New York, USA).

RESULTS

In total, 639 patients were evaluated for transplantation between 2009 and 2015. From these, 152 were removed from the data set as a result of having insufficient data or having an indicated CT. 33 had a CT prior to six months of the evaluation date and was ultimately excluded. A total of 454 underwent non-indicated CTs within six months of evaluation (71%) which comprised the final data set for further analysis. These 454 individuals had a mean age of 56.6, and of them 378 were on dialysis, 439 had a history of hypertension, 155 had a history of coronary artery disease or angina, 75 had a history of CHF, 64 had a history of cancer, 248 were diabetic, 68 had been transplanted prior, and 198 had a positive smoking history. There were no cases of thrombosis in the iliac vein or inferior vena cava.

Table 1: Distribution and p values of patient demographics and medical history; the total patient count is subdivided by positive findings for vascular calcification and waist list change.

| Total (n=454) | Vascular calcifications (n=60) | P value | Change in waitlist status (n=32) | P value |
|-----------|-------------------------------|---------|---------------------------------|---------|
| **Age**   |                               |         |                                 |         |
| Mean      | 56.6±1.1                      | 0.012   | 61.8±2.7                        | 0.010   |
| Range     | 19-84                         |         | 46-74                           |         |
| **BMI**   |                               | 0.287   | 0.495                           |         |
| Mean      | 29.4±0.5                      |         | 28.9±1.5                        |         |
| Range     | 16.1-76.9                     |         | 19.2-36.1                       |         |
| **Gender (%)** |                 | 0.408   | 0.624                           |         |
| Male      | 64.8                          |         | 68.8                            |         |
| Female    | 35.2                          |         | 31.2                            |         |
| **Dialysis (%)** |             | 0.460   | 0.247                           |         |
| Positive  | 83.3                          |         | 90.6                            |         |
| Negative  | 16.7                          |         | 9.4                             |         |
| **HTN (%)** |                       | 0.446   | 0.953                           |         |
| Positive  | 96.7                          |         | 96.9                            |         |
| Negative  | 3.3                           |         | 3.1                             |         |
| **CAD (%)** |                   | 0.001   | 0.006                           |         |
| Positive  | 34.1                          |         | 56.3                            |         |
| Negative  | 65.9                          |         | 33.7                            |         |
| **Cancer (%)** |              | 0.009   | 0.433                           |         |
| Positive  | 14.1                          |         | 18.8                            |         |
| Negative  | 85.9                          |         | 81.2                            |         |
| **DM type 2 (%)** |           | 0.002   | 0.042                           |         |
| Positive  | 54.6                          |         | 71.9                            |         |
| Negative  | 45.4                          |         | 22.1                            |         |
| **CHF (%)** |                     | 0.008   | 0.067                           |         |
| Positive  | 16.5                          |         | 28.1                            |         |
| Negative  | 83.5                          |         | 71.9                            |         |
| **Prior transplant (%)** |            | 0.434   | 0.535                           |         |
| Positive  | 15.0                          |         | 18.8                            |         |
| Negative  | 85.0                          |         | 81.2                            |         |
| **Smoking History** |           | 0.547   | 0.737                           |         |
| Positive  | 43.6                          |         | 44                              |         |
| Negative  | 56.4                          |         | 66                              |         |

*p<0.05 CHF: congestive heart failure; CAD: coronary artery disease; HTN: hypertension; BMI: body mass index; DM: diabetes mellitus
Table 2: P values detailing the significance of patient demographic information and past medical history resulting in either a CT finding, a diagnostic workup, a diagnostic workup finding, or any resulting change in waitlist status.

| Patient History | CT finding | Diagnostic workup | Diagnostic workup finding | Diagnostic workup leading to a change in waitlist status | CT finding leading to a change in waitlist status |
|-----------------|------------|-------------------|---------------------------|--------------------------------------------------------|-----------------------------------------------|
| Age             | 0.006*     | 0.042*            | 0.194                     | 0.502                                                  | 0.211                                         |
| BMI             | 0.868      | 0.436             | 0.592                     | 0.771                                                  | 0.559                                         |
| Gender          | 0.302      | 0.016*            | 0.242                     | 0.721                                                  | 0.559                                         |
| Dialysis        | 0.832      | 0.559             | 0.797                     | 0.131                                                  | 0.911                                         |
| HTN             | 0.235      | 0.484             | 0.935                     | 0.199                                                  | 0.417                                         |
| CAD             | 0.002*     | 0.872             | 0.856                     | 0.399                                                  | 0.001*                                        |
| Cancer          | 0.015*     | 0.418             | 0.25                      | 0.514                                                  | 0.229                                         |
| DM type 2       | 0.001*     | 0.166             | 0.504                     | 0.122                                                  | 0.015*                                        |
| CHF             | 0.002*     | 0.172             | 0.844                     | 0.666                                                  | 0.408                                         |
| Prior transplant| 0.556      | 0.314             | 0.591                     | 0.055                                                  | 0.442                                         |
| Smoker          | 0.507      | 0.041*            | 0.621                     | 0.828                                                  | 0.689                                         |

*p<0.05 CHF: congestive heart failure; CAD: coronary artery disease; HTN: hypertension; BMI: body mass index; DM: diabetes mellitus

Table 3: Total number of cases and p values detailing the significance of specific secondary medical conditions that were found during patient evaluation that resulted in a change to a patient’s waitlist status.

| Medical condition (CT finding) | Total number of cases | P value |
|--------------------------------|-----------------------|---------|
| Vascular calcification         | 60                    | <0.001* |
| Renal mass                     | 22                    | 0.662   |
| Pulmonary nodule               | 20                    | 0.001*  |
| IPMN                           | 3                     | 0.074   |
| Malignancy                     | 17                    | 0.004*  |

*p<0.05 IPMN: Intraductal papillary mucinous neoplasm.

Table 4: P values detailing the significance of specific secondary medical conditions that were found during patient evaluation resulting in further workup being ordered and resulting outcome and changes in waitlist status.

| Diagnostic workup | Diagnostic workup finding | Diagnostic workup leading to a change in waitlist status | CT finding leading to a change in waitlist status |
|-------------------|---------------------------|--------------------------------------------------------|-----------------------------------------------|
| Vascular calcification | 0.532 | 0.013* | 0.602 | <0.001* |
| Renal mass CT finding       | <0.001* | <0.001* | 0.717 | 0.071   |
| Pulmonary nodule CT finding | <0.001* | <0.001* | 0.086 | 0.34    |
| IPMN CT finding            | <0.001* | <0.001* | 0.651 | 0.224   |
| Malignancy CT finding       | <0.001* | <0.001* | 0.042* | 0.959   |

*p<0.05 IPMN: Intraductal papillary mucinous neoplasm.

CT findings

Of those 454, 121 (26.6%) had CT findings, 32 (7.0%) of which that resulted in waitlist status change. 18 of these 32 (56% of all CT findings) were permanently excluded due to significant vascular calcification. The presence of vascular calcification on CT (Table 1) was significantly associated with a history of coronary artery disease, cancer, diabetes, and congestive heart failure (p=0.001, 0.009, 0.002, and 0.008, respectively). The remaining 14 patients were excluded from transplant due to cardiac disease (1), presence of renal granuloma (1), pulmonary disease (2), cancer or masses (2 lung, 3 prostate, 2 unspecified), unspecified comorbidities (2), or unclear CT scan (1).

Variance in age was significant in relation to waitlist change with a p value of 0.01 (Table 1) and an average age of 61.81 (95% CI: 59.0-64.62). Whereas, patients who did not have a change in status had an average age of 56.64 (95% CI: 55.03-57.31). Coronary artery disease and diabetes mellitus were also significant factors with p values of 0.006 and 0.042, respectively (Table 1). Factors associated with vascular calcifications included age, coronary artery disease, cancer, diabetes mellitus, and congestive heart failure, with p values of 0.012, 0.001,
0.009, 0.002, 0.008, respectively (Table 1). Differences in age correlated with the presence of positive CT findings (p=0.006), with the average age of those having a CT finding at 59.21 (95% CI: 57.37-61.06), and those without at 55.60 (95% CI: 54.30-56.91) (Table 2). The total number of patients with each past medical history or demographic attribute is further categorized by those with that attribute having positive vascular calcifications or waitlist change, and those without the same attribute having positive calcifications or waitlist change.

**Diagnostic work up**

Sixty-one of the patients (13.5%) who received screening CTs necessitated further workup for incidental findings discovered, such as presence of renal mass, pulmonary nodule, vascular calcification, and findings suspicious for malignancy including intraductal papillary mucinous neoplasm (IPMN). Further workup for incidental findings included biopsy, MRI, chest X-ray, and urology consult. Coronary artery disease, cancer, diabetes mellitus, and congestive heart failure were all factors which correlated with positive CT findings, with p values of 0.002, 0.015, 0.001, 0.002, respectively (Table 2). Differences in age also correlated with needing further diagnostic workup after CT (p=0.042), with the average age of those undergoing workup at 60.07 (95% CI: 57.62-62.52), and those not at 56.06 (95% CI: 54.88-57.24). All patients who had a waitlist change were above the age of 45. However, a screening age cut-off of 45 would have resulted in 83.3% of our sample receiving a CT. A cut-off of ages above 50 would led to 94% of the findings that led to a waitlist change. A cut off age of 65 would have only led to 50% of the findings that led to a waitlist change but would have screened only 28% of the sample.

Male gender and history of smoking positively correlated with whether a patient received a workup, with p values of 0.016 and 0.041, respectively (Table 2). None of the factors tested correlated with a significant effect on whether a subsequent finding was discovered on a workup or whether that workup led to a waitlist change. However, the presence of coronary artery disease and/or diabetes mellitus correlated with CT findings that led to a waitlist change in status for renal transplantation, with p values of 0.001 and 0.015, respectively (Table 2).

The presence of vascular calcifications, pulmonary CT findings, and findings of malignancy on CT all correlated with an increased incidence of permanent waitlist status change, with p values of <0.001, <0.001, 0.004, respectively (Table 3). The presence of renal mass, pulmonary nodules, IPMN, or other malignant finding on CT all correlated with an increased number of additional workups with p values all below 0.001 (Table 4). However, the presence of malignancy on CT was the sole variable that correlated with waitlist change due to subsequent workups with a p value of 0.042. Furthermore, the presence of vascular calcifications was the only finding from a CT alone that led to a waitlist status change for renal transplant patients, with a p value of <0.001 (Table 4). Twenty cases of pulmonary nodules found on CT were noted. Sixteen were followed with corresponding diagnostic workup, of which eight were positive. Those patients with a pulmonary nodule finding on CT were likely to be removed from the waitlist, primarily due to the initial CT finding, not the workup findings (Table 4). Notably, of the 22 patients with a finding of renal mass on screening CT, 19 (86.4%) received a subsequent ultrasound for further diagnostic assessment, of which 12 had a positive workup finding resulting in permanent waitlist status change.

**DISCUSSION**

All prospective kidney transplant recipients undergo a comprehensive evaluation to determine eligibility for transplantation and to maximize outcomes. Current guidelines advise an exhaustive list of recommendations to determine the eligibility with regards to age, obesity, presence of malignancy, diabetes, cardiovascular disease, and peripheral vascular disease. Despite recommending a battery of tests or imaging for each area of assessment, most medical professionals lack guidance on the use of routine imaging for screening or what criteria should be considered for inclusion in such screening imaging. This stands in contrast to others such as Harmath et al., who stress that pre-transplant imaging evaluation is a universal requirement for all potential recipients to obtain preoperative knowledge of anatomy and to detect conditions that would contraindicate transplantation. They suggest CT imaging in patients with significant risk factors for peripheral arterial disease (PAD), including smoking and diabetes mellitus. Our institution employs a similar approach by utilizing screening CT imaging in all transplant candidates under evaluation. Clarifying this gap in understanding by quantifying the role of CT in renal transplant evaluation and identifying characteristics that could guide its use is the goal of the investigation.

Of the renal transplant candidates receiving screening CT imaging, only 7.0% were permanently withdrawn from the waitlist due to findings uncovered on imaging. Advanced age, coronary artery disease (CAD), and diabetes mellitus (DM) were the only factors significantly predictive of CT driven exclusion from the waitlist (p=0.01, 0.006, and 0.042, respectively) is easily interpreted. Age and diabetes are risk factors for vascular calcification and coronary artery disease, a contraindication to transplantation in the setting of advanced disease. Approximately 48.8% of patients receiving any form of renal replacement therapy are over the age of sixty-five. Considering that the data shows that with increasing age, CT is more likely to detect pathology that preclude transplantation, screening this group with imaging is critical. Arterial wall calcification is known to be a consistent and strong predictor of cardiovascular events in those with
chronic renal insufficiency. It is often indicative of poor cardiovascular health. This is important considering that ischemic heart disease is the leading cause of death in the post-transplant period. Furthermore, there is concern that the presence of significant vascular calcification complicates intraoperative vascular anastomosis. Risk factors for its development include advancing age, cigarette smoking, diabetes mellitus, as well as dialysis. Its prevalence exceeds 80% in dialysis patients, compared to 47-83% in non-dialysis patients. Of the candidates in this study whose CT findings led to a permanent exclusion from the waitlist, a majority (56%, or 18 patients) were withdrawn due to the presence of significant vascular calcification.

The discovery of vascular calcification on CT imaging was significantly associated with a history of coronary artery disease, cancer, diabetes, and congestive heart failure (p=0.001, 0.009, 0.002, and 0.008, respectively). Age, coronary artery disease, diabetes, and congestive heart failure may thus be used in selecting transplant candidates who receive CT during the evaluation. Supporting this approach for a more conservative imaging protocol is Aitken et al, who challenge notions concerning proposed intra- and postoperative risks posed by vascular calcification and suggest an alternative approach towards screening. They indicate that young patients with no history of diabetes or smoking may be spared preoperative imaging or can be assessed with simple ankle-brachial pressure index measurements. Conversely, asymptomatic candidates with risk factors for vascular calcification (advancing age, abnormal pulses on examination, diabetes, smoking) in addition to calcification on pelvic x-rays may prompt further imaging in the form of CT angiography. This helps untangle the ambiguity in current guidelines regarding the optimal preoperative imaging technique to assess vascular calcification, which differ among American, Canadian, and European guidelines. This study is consistent with the findings of Davis et al, who found that advanced age and diabetes mellitus to be independently predictive of higher calcification morphology scores and thus most appropriate in choosing at-risk populations in need of CT screening. Likewise, a novel CT-based calcification score developed by Kahn et al confirm age as the strongest risk factor for media sclerosis.

In our experience, the universal use of screening CT was associated with the discovery of incidental findings, such as vascular calcifications, pulmonary nodules, and malignancy, which led to additional workup. In most instances (89 of 121, or 73.6%), the outcome of this additional workup was unremarkable and benign, not changing the waitlist status, but rather, exposed patients to unnecessary radiation and burdening them with additional medical costs. Only the finding on screening CT suspicious for malignancy was significantly associated with additional workup whose results changed waitlist status. With only three cases of IPMN in the dataset, no firm conclusion can be drawn from this. In addition, while renal masses were discovered incidentally on CT in 22 patients, ultrasound imaging was performed afterwards in 19 (86.4%) of these to gather further diagnostic information. Considering the extent to which screening CTs led to unnecessary radiation exposure and superfluous workup, this data supports the notion of targeting the use of screening CT imaging based on patient history, limiting subsequent workup and imaging depending on the specific incidental finding from the initial CT, and use of other imaging modalities, such as ultrasound.

Strengths of this study include the breadth of demographic and medical history variables included in the analysis. As an academic teaching hospital, the sample of patients treated represents the broad demographics of a large population. However, the investigation was limited by its sample size. This drawback was augmented by the limitation that records were obtained from only one institution. Furthermore, some records were deficient and incomplete. For example, information could not be obtained on length of patient history of diabetes, dialysis, or other conditions. The records present in the institution’s electronic medical record and additional data may have been overlooked. Another limitation of this study was that it was collected retrospectively.

The role of computed tomography studies in the evaluation of renal transplant candidates is ill defined. Without a universal protocol regarding pre-transplant imaging, medical professionals and institutions are left to their own distinct policies and previous experiences with transplant candidates. These unique policies are bound to lead to further unwarranted testing, increasing patient burden. Furthermore, increased costs and risks to health from radiation exposure are associated with unnecessary medical imaging, the majority of which stems from CT imaging. This paper is the first to quantify the frequency by which CT imaging in renal transplant candidate evaluation leads to exclusion from the renal transplantation waitlist. It corroborates findings in the literature that suggest a blanket use of CT screening in the renal pre-transplant evaluation is unwarranted. A more conservative preoperative assessment protocol by selecting only high-risk patients for imaging may be more effective. These patients with advanced age, coronary artery disease, and diabetes mellitus are more likely to present with CT findings, especially vascular calcification, that contraindicate renal transplantation.

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