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# Dual-Energy X-Ray Absorptiometry-Derived Advanced Hip Analysis and the Trabecular Bone Score Are Associated With the Diagnosis of Fracture Following Kidney and Simultaneous Pancreas-Kidney Transplantation

Tahira Scott[1,2] | Jasna Aleksova[3,4] | Carmel Hawley[1,2,5,6] | Mina Khair[1,2] | Harpreet Kaur[7] | Christopher Schultz[8] | Ryan Gately[1,2] | Mirna Vucak-Dzumhur[7,9] | James Elhindi[10] | Grahame J. Elder[7,9,11]

[1]Department of Nephrology, Level 2, ARTS Building, Princess Alexandra Hospital, Woolloongabba, Brisbane, Queensland, Australia | [2]School of Medicine, University of Queensland, Brisbane, Australia | [3]Department of Medicine, Monash University, Clayton, Victoria, Australia | [4]Department of Endocrinology, Monash Health, Melbourne, Australia | [5]Australasian Kidney Trials Network, University of Queensland, Brisbane, Australia | [6]Translational Research Institute, Brisbane, Australia | [7]Department of Renal Medicine, Westmead Hospital, Westmead, New South Wales, Australia | [8]Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital, Central Adelaide Local Health Network, Adelaide, South Australia, Australia | [9]University of Notre Dame Medical School, Sydney, Australia | [10]Research and Education Network, Western Sydney Local Health District, Westmead, New South Wales, Australia | [11]University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia

**Correspondence:** Grahame J. Elder (grahame.elder@health.nsw.gov.au)

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## ABSTRACT

**Background:** Patients with kidney failure have elevated fracture risk that remains high following kidney transplantation. This study aimed to assess whether dual-energy x-ray absorptiometry-derived advanced hip analysis (AHA) and the trabecular bone score (TBS) improve bone mineral density (BMD)-based post-transplant fracture prediction.

**Methods:** Patients receiving kidney-only or simultaneous pancreas-kidney (SPK) transplants underwent immediate post-transplant dual-energy x-ray absorptiometry to provide BMD, the TBS, and AHA parameters; femoral neck, calcar, and shaft cortical thickness (CTh), and femoral neck buckling ratio (BR), an index of structural instability. Patients received treatment to reduce post-transplant BMD loss, using an established risk algorithm. Hazard ratios were determined using Kaplan–Meier and Cox proportional hazard models.

**Results:** Of 357 transplant recipients, 289 (83%) received a kidney-only transplant. There were 83 incident fractures over a median of 4.4 years (IQR: 2.5–5.5). Fracture was associated with type 1 diabetes mellitus ($p < 0.001$), former smoking ($p = 0.006$), lower 25-hydroxyvitamin D ($p = 0.003$), BMD at total proximal femur and neck of femur ($p < 0.001$) and spine ($p = 0.008$), lower CTh at the calcar ($p = 0.005$) and shaft ($p = 0.023$), higher BR ($p = 0.016$) and lower TBS ($p = 0.047$). Following multivariable adjustment, type 1 diabetes mellitus, 25-hydroxyvitamin D, smoking, and femoral neck BMD remained significant. Using the BMD-based risk algorithm, inclusion of the BR improved the model fit.

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**Conclusion:** BMD, the TBS, and AHA parameters are associated with incident fracture in kidney-only and SPK transplant recipients. Pre-transplant smoking, lower 25-hydroxyvitamin D and BMD are potentially modifiable factors that could reduce post-transplant fracture risk.

## 1 | Introduction

Kidney transplant recipients have a risk of incident fracture within the first three post-transplant years that is approximately five-fold greater than the general population [1–3]. This elevated fracture risk is sustained, and in patients with a functioning graft, remains 2-fold greater than that of the general population for up to 15 years [2]. The term chronic kidney disease-mineral and bone disorder (CKD-MBD) encompasses biochemical and hormonal abnormalities affecting bone and mineral metabolism, vascular calcifications, and renal osteodystrophy, which persists after transplantation and contributes to heightened risks for fracture, cardiovascular events, and mortality. Other factors likely to influence post-transplant fracture include glucocorticoid exposure, dialysis vintage, and sex hormone deficiency, which may improve after transplantation [3]. Risk factors shared with the general community include low bone mineral density (BMD) and osteoporosis, prevalent fracture, female gender, diabetes mellitus, and advanced age [1, 2, 4, 5].

Assessing fracture risk and identifying kidney transplant recipients who may benefit from pharmacological interventions remains a challenge. Inappropriate prescription of anti-resorptive therapy may induce or perpetuate low bone turnover or adynamic bone. The fracture risk assessment tool (FRAX) has not been validated in kidney transplant recipients, and is likely to underestimate fracture risk [6]. BMD assessed by dual-energy x-ray absorptiometry (DXA) is recommended post-transplant, but the association of BMD by DXA and incident fractures has been characterized as rather weak, and not consistent across skeletal sites [7]. The ability of DXA to assess changes in bone microarchitecture and distinguish age-related low BMD from renal osteodystrophy is also limited. The gold standard for determining the cause of renal osteodystrophy remains tetracycline-labeled bone trephine and histomorphometry, but this has poor contemporary uptake due to diminishing clinical expertise, delays in diagnosis, and reluctance to perform repeat biopsies [8]. Therefore, improved non-invasive techniques for predicting post-transplant fracture risk are required.

High-resolution peripheral quantitative computer tomography [9] and micro-magnetic resonance imaging (MRI) [10] are promising tools, but are generally inaccessible, expensive, and have restricted normative population data. By comparison, DXA is relatively inexpensive and widely available. In addition to BMD, DXA can be used to derive structural parameters that may inform fracture risk. The trabecular bone score (TBS), an indirect measure of trabecular microarchitecture derived from grey-scale textural evaluation of lumbar spine DXA images, has been included in the fracture risk assessment tool FRAX to improve fracture prediction in the general population. DXA images can also be analyzed using readily available "advanced hip analysis" (AHA) software, to calculate cortical thickness (CTh) at the femoral neck, the intertrochanteric region (calcar), and femoral shaft, and indices of deformation and structural capacity of the bone under differing loads. The femoral neck buckling ratio (BR) is an indicator of structural instability, calculated by dividing the femoral neck radius by its CTh. We have previously reported that compared to the general population, the TBS, cortical parameters, and BR are abnormal in patients with kidney failure (KF), particularly those with type-1 diabetes mellitus (T1DM), and abnormalities of these parameters are associated with prevalent fracture in KF patients [5, 11, 12].

No studies have yet examined associations between the TBS, AHA indices, demographic and laboratory data, and post-transplant incident fracture in patients undergoing kidney-only (KO) or simultaneous pancreas-kidney (SPK) transplants. Therefore, the aim of this retrospective observational study was to assess DXA-derived BMD, TBS, AHA indices, demographic and laboratory data at the time of transplantation, and to determine which factors are associated with post-transplant incident fracture. A secondary aim was to assess the effect of anti-resorptive therapy during the first post-transplant year on change in BMD and the TBS.

## 2 | Methods

Consecutive patients with KF undergoing KO or SPK transplantation were included in this study. Patients were from two Australian transplantation centers, Princess Alexandra Hospital (PAH) in Queensland and Westmead Hospital (WH) in New South Wales. Most patients remained under the care of these centers beyond the acute transplant phase.

Patient recruitment differed slightly between the sites. The PAH group included individuals who received a kidney transplant from September 2015 to May 2021, with a censor date of December 2021. Participants were required to provide consent to be enrolled in the study and to undergo a telephone questionnaire to identify their fracture history. The WH group enrolled patients who underwent either a KO or SPK transplant from April 2015 to March 2018, with a censor date of October 2022. Patient consent was not required before recruitment, because incident and prevalent fracture history data was routinely collected for clinical management and was recorded in the electronic medical record. Figure 1 provides a flow diagram of patient recruitment.

Ethical approval for this study was obtained from the Central Queensland Hospital and Health Service Human Research Ethics Committee (HREC2020QCQ60860) for PAH and from the Western Sydney Local Health District Human Research Ethics Committee (2019/ETH02382 with General Amendment 55735; August 2021). The study was conducted in accordance with STROBE guidelines [13].

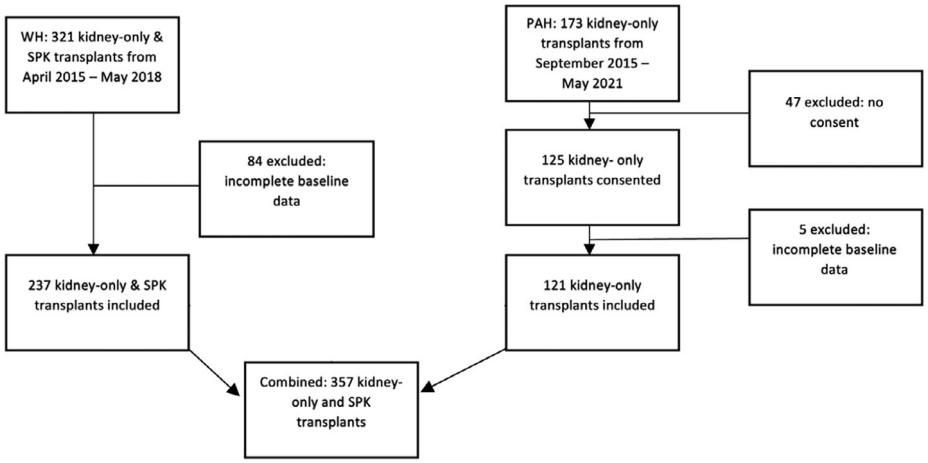


**FIGURE 1** | Study flow (1) Westmead hospital (WH) and (2) Princess Alexandra hospital (PAH).

## 2.1 | Demographics, Immunosuppressive Therapy, and Surgical Technique

Demographic information, history of diabetes mellitus, smoking status, dialysis vintage and prior glucocorticoid use for greater than 3 months, and other bone modifying medications (calcium, vitamin D, calcitriol, bisphosphonates, cinacalcet or hormone replacement therapies) were recorded from electronic records. Patients at both centers were treated with immunosuppressive protocols that included low-dose glucocorticoids. Briefly, both kidney and SPK transplant recipients were treated with tacrolimus, mycophenolate, and prednisolone, with basiliximab used for induction for low and moderate-risk KO recipients. Antithymocyte globulin was used for the induction of high-risk KO recipients and all SPK recipients. Moderate and high-risk KO recipients and all SPK recipients were targeted to slightly higher trough tacrolimus levels than low-risk kidney recipients, with 12-month targets being 6–8 versus 5–7 ng/mL. The dosing of mycophenolate did not differ. Initial glucocorticoid dosing was hydrocortisone 100 mg IV bd until oral dosing was tolerated, then oral prednisolone 20 mg daily for 1 month, then reducing by 2.5 mg every 2 weeks to 10 mg daily. Further reductions were based on protocol biopsy results. Long-term, the lowest daily prednisolone dose for KO patients was 5–7.5 mg, and for SPK patients 7.5 mg. SPK arterial and venous anastomoses were to the iliac vessels, and all drainage was enteric, with the jejunal end of the transplanted duodenum anastomosed end to side to the anti-mesenteric border of an adjacent loop of small bowel.

## 2.2 | Laboratory Data

Fasting blood samples were collected immediately pre-transplant, with analyses conducted at the laboratories of both major hospitals. Serum calcium, phosphate, magnesium, creatinine, and ALP were assayed using the Siemens Vista & Atellica platform (Siemens Healthcare GmbH). Serum 25OHD was measured using the Liaison assay (DiaSorin Inc., Stillwater, MN, USA) and $1,25(OH)_2D$ by radioimmunoassay (DiaSorin Inc.) Intact PTH was measured using the Abbott Architect (Abbott Diagnostics) at WH and Siemens Atellica immunoassay at PAH. The bone turnover markers procollagen type 1 N-terminal propeptide (P1NP), and the cross-linked C-terminal telopeptide of type 1 collagen (CTX) were analyzed on the Roche platform e411 at WH and Roche e602 and e801 at PAH, respectively (Roche Diagnostics). HbA1c was measured using the Siemens Atellica enzymatic method at WH and Biorad D10 at PAH. These blood were recollected at 4- and 12-weeks post-transplant.

## 2.3 | Imaging Parameters

DXA imaging was performed at both WH and PAH, using GE Lunar iDXA narrow-angle fan beam bone densitometers (Encore version 16) at the lumbar spine, femoral neck, one-third radius, a site of predominantly cortical bone, and ultra-distal (UD) radius. DXA examinations were scheduled as soon as practicable after transplantation, and always within 4 weeks. Follow-up DXAs were performed 12 months after transplantation.

Australian Geelong/Lunar population reference data [14] were used to calculate *T*-scores, representing the number of standard deviations (SD) above or below mean BMD values of young adults, and Z-scores, representing the number of SDs above or below mean BMD values for individuals of the same age and sex. TBS values were obtained using TBS Insight Software (version 2.1.2.0; Medimaps, Merignac, France). TBS values >1.31 were considered consistent with preserved trabecular microarchitecture, from 1.21 to 1.31, consistent with intermediate loss of trabecular microarchitecture, and <1.21 consistent with a significant reduction in microarchitectural integrity [15]. AHA parameters were derived using software developed for GE Lunar DXA hip images, applying modeling initially developed by Beck et al. [16]. Reference ranges were derived by analysis of hip images from the Australian population-based Geelong Osteoporosis Study, as previously described [11]. For the GE-Lunar iDXA bone densitometer, the quoted coefficient of variation (CV) for areal BMD is <2% for the spine, hip, forearm, and TBS. However, the CV for CTh and the BR is less precise at around 4% and 5.6%, respectively [17].

## 2.4 | Fractures

At WH, lateral thoracolumbar x-rays were performed as soon as practicable after transplantation, and always within 4 weeks.

Any fracture detected was designated a prevalent vertebral fracture. Lateral spine x-rays were repeated at 1- and 3-years post-transplant. Fractures were defined by ≥20% loss of vertebral height using the criteria of Genant et al. [18]. Non-clinical vertebral fractures were not assessed at PAH. At both sites, minimal trauma, non-vertebral fractures post-transplant were determined through clinical history and corroborated with imaging and radiological reports.

### 2.5 | Study Outcomes

The primary outcomes of the study were to assess whether post-transplant fracture was associated with baseline TBS and AHA parameters; the BR and CTh at the femoral neck, calcar, and femoral shaft, censored for death, graft failure, loss to follow-up and end of study.

Secondary outcomes were to examine associations between post-transplant fracture and baseline BMD at spine, hip, and forearm sites, demographic data, prevalent fracture, and pre-transplant laboratory data. An additional secondary outcome was to assess the effect of bisphosphonates use, allocated using an established treatment algorithm [6, 19], on changes in BMD and the TBS over the first post-transplant year.

### 2.6 | Statistical Analysis

Patient characteristics were expressed as frequency and percentages for categorical variables and median (interquartile ranges) for non-normally distributed continuous variables. Chi-squared (for categorical variables) and the Wilcoxon sign rank test (for non-normally distributed continuous variables) were used to assess differences between cohorts. Time-to-event analyses of recipients with incident fragility fractures versus no fragility fractures were evaluated by Kaplan–Meier survival analysis using the log-rank test.

Univariable and multivariable Cox proportional hazard models were used for survival analyses. Covariates with a $p$ value <0.2 in the univariable model were included in the multivariable model. High/low BRs were defined as above/below the sample median as the least biased estimator. The model's goodness of fit was compared by Akaike information criterion, by comparing two models with and without the BR and TBS scores. Statistical analysis was performed by R studio version 2022.12.0 + 353 (Vienna, AT) software. $p$ values <0.05 were deemed statistically significant. More complex analyses, including death as a competing risk, were not included due to study numbers.

## 3 | Results

### 3.1 | Baseline Characteristics

The study included 357 transplant recipients, 289 (83%) of whom received a KO transplant and 68 (17%) a SPK transplant. The mean age at transplantation was 48 ± 13 years, with 62% male and 55% of Caucasian ethnicity. The median dialysis vintage before transplant was 29 months (IQR: 11–51). T1DM was present in 20% of the cohort. Patient characteristics are indicated in Table 1. Differences between patients with and without type 1 diabetes mellitus are included in Table S1.

### 3.2 | Post-Transplant Fracture

The median follow-up was 4.4 years (IQR: 2.4–5.6), comprising KO 4.5 years (IQR: 2.7–5.6) and SPK 3.1 years (IQR: 1.1–5.2). During the study period, there were 83 incident fractures, 68% of which occurred after KO and 32% after SPK transplantation, equivalent to 58 fractures per 1000-person years: 147/1000 patient years for patients with T1DM and 39/1000 patient years for the remainder. During the follow-up period, 27 patients died. Fracture sites are indicated in Table 2. A single facial fracture was not included in the analyses.

By AHA, lower CTh at the femoral neck, calcar, and shaft and higher BRs were associated with post-transplant fracture but the TBS was not. Post-transplant fracture was also associated with lower baseline BMD $T$-scores at the lumbar spine, femoral neck, total proximal femur, and ultra-distal radius but not with BMD at the 1/3 radius.

As indicated in Table 1, fractures occurred more commonly in patients with prevalent (pre-transplant) fracture ($p = 0.020$), T1DM ($p < 0.001$), and former or current smokers ($p = 0.005$). Serum biochemistry was similar in patients who did or did not sustain a post-transplant fracture, except for an association of lower values of 25-hydroxyvitamin D and fracture ($p = 0.039$).

### 3.3 | Univariable and Multivariable Cox Proportional Hazard Analyses

In univariable Cox proportional hazard model analysis DXA-derived parameters associated with fracture were BR above the median (HR 1.05, 95% CI 1.01–1.08, Figure 2A), CTh below the median at the calcar (HR 1.35, 95% CI 1.08–1.66, Figure 2B) and shaft (HR 1.17, 95% CI 1.02–1.36, Figure 2C), femoral neck $T$-score (HR 1.72, 95% CI 1.38–2.12, Figure 2D), total proximal femur $T$-score (HR 1.56, 95% CI 1.31–1.88), lumbar spine $T$-score (HR 1.20, 95% CI 1.04–1.36) and ultra-distal radius $T$-score (HR 1.21, 95% CI 1.06–1.4), and TBS below the median value (HR 5.55, 95% CI 1.03–33.3). CTh at the femoral neck ($p = 0.092$) and the TBS assessed by tertiles <1.21, 1.21–1.31, and >1.31 ($p = 0.08$) were not significantly associated with fracture.

Fracture was also associated with current/former smoking (Hazard ratio [HR] 1.89, 95% CI 1.20–2.97), T1DM (HR 3.26, 95% CI 2.10–5.06, Figure S1), and serum 25-hydroxyvitamin D levels < 50 nmol/L (HR 2.01, 95% CI 1.29–3.14) (Table 3).

After adjustment for dialysis vintage, smoking status, T1DM, prevalent fracture, serum 25-hydroxyvitamin D, the BR, TBS and femoral and lumbar $T$-score, T1DM (HR 2.50, 95% CI 1.43–4.36), 25-hydroxyvitamin D <50 pmol/L (HR 1.76, 95% CI 1.04–2.98), smoking status (HR 1.75, 95% CI 1.06–2.91) and the femoral neck $T$-score (HR 1.63, 95% CI 1.19–2.27) remained significantly associated with fracture (Table 3 Multivariable Model 1).

**TABLE 1** | Associations of baseline patient characteristics, imaging parameters, pre-transplant medications and laboratory values with incident fracture.

| Patient characteristic | Overall, $N = 357$[a] | No incident fracture, $N = 274$[a] | Incident fracture, $N = 83$[a] | $p$ value[b] |
|---|---|---|---|---|
| **Prevalent fracture (within 10 years)** | | | | 0.020 |
| Yes | 135 (40%) | 94 (36%) | 41 (51%) | |
| No | 206 (60%) | 166 (64%) | 40 (49%) | |
| Age at transplant (years) | 48 (13) | 48 (13) | 47 (12) | 0.6 |
| Gender | | | | 0.8 |
| Female | 137 (38%) | 104 (38%) | 33 (40%) | |
| Male | 220 (62%) | 170 (62%) | 50 (60%) | |
| Ethnicity | | | | 0.020 |
| Caucasian | 196 (55%) | 141 (51%) | 55 (66%) | |
| Asian | 43 (12%) | 39 (14%) | 4 (4.8%) | |
| Other | 118 (33%) | 94 (34%) | 24 (29%) | |
| BMI ($kg/m^2$) | | | | 0.3 |
| (0, 18) | 7 (2.1%) | 5 (1.9%) | 2 (2.5%) | |
| (18, 25) | 103 (30%) | 73 (28%) | 30 (38%) | |
| (25, 30) | 100 (30%) | 82 (32%) | 18 (23%) | |
| (30, 60) | 128 (38%) | 99 (38%) | 29 (37%) | |
| Dialysis vintage (months) | 28 (11, 51) | 25 (10, 48) | 30 (13, 52) | 0.4 |
| Current/former smoking | | | | 0.005 |
| Yes | 151 (45%) | 106 (40%) | 45 (58%) | |
| No | 188 (55%) | 156 (60%) | 32 (42%) | |
| Type one diabetes mellitus | | | | <0.001 |
| Yes | 69 (20%) | 36 (14%) | 33 (40%) | |
| No | 278 (80%) | 228 (86%) | 50 (60%) | |
| Simultaneous kidney and pancreas transplant | | | | <0.001 |
| Yes | 59 (17%) | 33 (12%) | 26 (32%) | |
| No | 289 (83%) | 233 (88%) | 56 (68%) | |
| Type two diabetes mellitus | | | | 0.4 |
| Yes | 67 (19%) | 54 (20%) | 13 (16%) | |
| No | 278 (81%) | 210 (80%) | 68 (84%) | |
| **Pre-transplant medications** | | | | |
| Calcium carbonate | | | | 0.2 |
| Yes | 134 (54%) | 97 (51%) | 37 (62%) | |
| No | 116 (46%) | 93 (49%) | 23 (38%) | |
| Calcitriol | | | | 0.2 |
| Yes | 145 (59%) | 116 (61%) | 29 (51%) | |
| No | 101 (41%) | 73 (39%) | 28 (49%) | |
| Cinacalcet | | | | >0.9 |
| Yes | 29 (8.6%) | 22 (8.5%) | 7 (9.0%) | |
| No | 307 (91%) | 236 (91%) | 71 (91%) | |
| Bisphosphonates | | | | 0.055 |
| Yes | 15 (4.4%) | 8 (3.1%) | 7 (8.8%) | |
| No | 324 (96%) | 251 (97%) | 73 (91%) | |

(Continues)

**TABLE 1** | (Continued)

| Patient characteristic | Overall, $N = 357$[a] | No incident fracture, $N = 274$[a] | Incident fracture, $N = 83$[a] | $p$ value[b] |
|---|---|---|---|---|
| Hormonal therapy or OCP | | | | 0.7 |
| Yes | 11 (9.2%) | 9 (8.9%) | 2 (11%) | |
| No | 109 (91%) | 92 (91%) | 17 (89%) | |
| Glucocorticoids > 3 months | | | | 0.5 |
| Yes | 60 (18%) | 44 (17%) | 16 (20%) | |
| No | 278 (82%) | 215 (83%) | 63 (80%) | |
| **Pre-transplant laboratory parameters** | | | | |
| Corrected calcium (mmol/L) | 2.31 (0.18) | 2.30 (0.18) | 2.33 (0.19) | 0.3 |
| Phosphate (mmol/L) | 1.68 (0.59) | 1.71 (0.59) | 1.60 (0.58) | 0.14 |
| Magnesium (mmol/L) | 0.92 (0.19) | 0.92 (0.19) | 0.94 (0.18) | 0.3 |
| Alkaline phosphatase (U/L) | 115 (80) | 112 (82) | 124 (76) | 0.093 |
| 25-hydroxyvitamin D (nmol/L) | 72 (35) | 73 (34) | 66 (36) | 0.039 |
| Intact parathyroid hormone (pmol/L) | 60 (53) | 61 (52) | 60 (55) | 0.7 |
| Procollagen-type 1 N-terminal propeptide (μg/L) | 384 (396) | 379 (397) | 401 (393) | 0.4 |
| C-terminal-telopeptide (ng/L) | 1944 (1540) | 1923 (1542) | 2009 (1542) | 0.4 |
| **Imaging parameters** | | | | |
| Trabecular bone score | 1.33 (1.26, 1.41) | 1.34 (1.26, 1.42) | 1.32 (1.22, 1.39) | 0.10 |
| Cortical thickness femoral neck (mm) | 2.98 (2.17, 4.46) | 3.06 (2.23, 4.58) | 2.46 (1.78, 3.74) | 0.011 |
| Cortical thickness femoral calcar (mm) | 3.42 (2.89, 4.25) | 3.50 (2.96, 4.36) | 3.02 (2.67, 3.77) | <0.001 |
| Cortical thickness femoral shaft (mm) | 4.97 (3.90, 5.71) | 5.10 (4.00, 5.83) | 4.50 (3.67, 5.42) | 0.004 |
| Buckling ratio | 6.1 (3.7, 8.8) | 5.7 (3.5, 8.2) | 7.4 (4.8, 10.0) | 0.003 |
| Lumbar spine *T*-score | −0.70 (−1.70, 0.50) | −0.50 (−1.60, 0.70) | −1.25 (−1.80, −0.10) | 0.006 |
| Femoral neck *T*-score | −1.50 (−2.20, −0.60) | −1.30 (−2.00, −0.50) | −2.00 (−2.70, −1.50) | <0.001 |
| Total proximal femur *T*-score | −1.30 (−2.10, −0.30) | −1.10 (−1.85, −0.20) | −2.10 (−2.50, −1.10) | <0.001 |
| Ultra-distal radius *T*-score | −1.60 (−2.70, −0.20) | −1.50 (−2.50, 0.00) | −2.25 (−3.40, −0.93) | 0.002 |
| 1/3 radius *T*-score | −1.01 (1.16) | −1.00 (1.18) | −1.04 (1.09) | 0.8 |

*Notes:* Values are expressed as frequency (percentage) for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median (interquartile ranges) for non-normally distributed continuous variables. BMI, body mass index; OCP, oral contraceptive pill; BMD, bone mineral density. Forearm BMD was not collected from the Brisbane cohort. Data on the variables was missing for the following percentage (%) of recipients; prevalent fracture 4%, BMI 5.3%, dialysis vintage 5.3%, smoking status 5%, type one and two diabetes mellitus 3.3%, calcium carbonate 29%, calcitriol 31%, cinacalcet 5.8%, bisphosphonates 5%, hormonal therapy or OCP 27%, glucocorticoids 5.3%, serum calcium, phosphate and ALP all 0.28%, serum magnesium 0.8%, vitamin D 7%, PTH 3.3%, procollagen-N-terminal-peptide 4.4%, Beta-C-terminal-telopeptide 6.7%, trabecular bone score 1.6%, cortical thickness neck and buckling ratio 1.4%, cortical thickness calcar 1.6%, cortical thickness shaft 2%, lumbar BMD and Z score 0.02%, lumbar *T* score 1.6%, femoral BMD and Z score 0.5%, femoral *T* score 1.9%, total proximal hip BMD and Z score 0.5%, total proximal hip *T* score 1.9%, ultra-distal radius BMD 31%, ultra-distal radius *T* and Z score 32%, 1/3 radius BMD 31% and 1/3 radius *T* and Z score 32%. There were varying follow-up times in years for both the incident fracture group (median of 4.8 years; IQR 3.56–5.69) and the non-incident fracture group (median 2.08 years; IQR 0.72–3.08).

[a] *n* (%); mean (SD).

[b] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

A sub-analysis with the exclusion of T1DM, which included 278 transplant recipients with 50 fractures, was completed. After adjustment in the multivariable model for smoking status, past glucocorticoid exposure, TBS and femoral and lumbar spine *T*-scores, smoking status (HR 1.88, 95% CI 1.04–3.41), and femoral neck *T*-score (HR 1.40, 95% CI 0.99–2) remained associated with fracture.

### 3.4 | Responses to Bisphosphate Therapy

Using an established algorithm [19], individuals considered to have a high fracture risk, with lower BMD *T*-scores and normal or elevated bone turnover markers and PTH on their 4-week and 12-week laboratory data, were treated with bisphosphonate therapy, with the aim to reduce loss of BMD. This resulted in

**TABLE 2** | Sites of incident fracture.

| Site of fracture | Overall *N* | T1DM | Non T1DM |
|---|---|---|---|
| Upper limb (UL) | 12 | 1 | 11 |
| Carpal | 4 | 0 | 4 |
| Non-carpal | 8 | 1 | 7 |
| Lower limb (LL) | 39 | 20 | 19 |
| Metatarsal | 10 | 6 | 4 |
| Non-metatarsal | 29 | 24 | 15 |
| Vertebral | 11 | 5 | 6 |
| Clavicle | 2 | 0 | 2 |
| Rib | 11 | 3 | 8 |
| Multi-site fracture | 8 | 4 | 4 |
| | $N = 83$ | | |

169 patients commencing bisphosphonate therapy by 3 months post-transplant. These high-risk patients had significant improvements in BMD at 12 months at the lumbar spine of 4% (IQR: −7 to 16; $p < 0.001$) and total proximal femur of 2% (IQR: −2 to 5; $p = 0.023$) and a non-significant improvement in the TBS of 2% (IQR: −4 to 7; $p = 0.084$) (Table S2). Recipients considered at lower risk, and not treated with bisphosphonates, had no change in TBS or other BMD parameters, except at the lumbar spine, where there was a significant loss of BMD −2% (IQR: −13 to 5; $p < 0.001$). The algorithm effectively predicted fracture risk, with allocation to therapy based on the algorithm associated with an increased incidence of fragility fracture (Figure S2). BRs above the median value were associated with higher fracture risk and lower BRs were associated with lower fracture risk. When BRs above or below the median were added to the risk algorithm as an interaction parameter, fracture risk discrimination was improved in those patients considered at low risk but with a high BR, or high risk but with a low BR; (HR 2.36, 95% CI 0.96, 5.80; $p = 0.06$, Figure S3). The addition of the BR might, therefore, influence the management of some patients who were borderline for antiresorptive therapy.

## 4 | Discussion

We have previously reported that the TBS and AHA parameters were associated with prevalent fracture in patients on dialysis [5, 11, 12]. The current study extends those results, showing DXA-derived AHA parameters and the TBS, assessed close to the time of transplantation, are associated with incident fracture after KO and SPK transplantation. In univariate analyses, the baseline BR was higher, and CTh and the TBS were lower in patients who suffered post-transplant fractures. In addition, baseline BMD at all sites except the 1/3 radius was associated with post-transplant fracture. Lack of association at the 1/3 radius may relate to differential effects of age, T1DM, time on dialysis, and particularly hyperparathyroidism at appendicular skeletal sites of predominantly cortical bone [20]. Several earlier studies support the use of BMD and the TBS to stratify fracture risk in

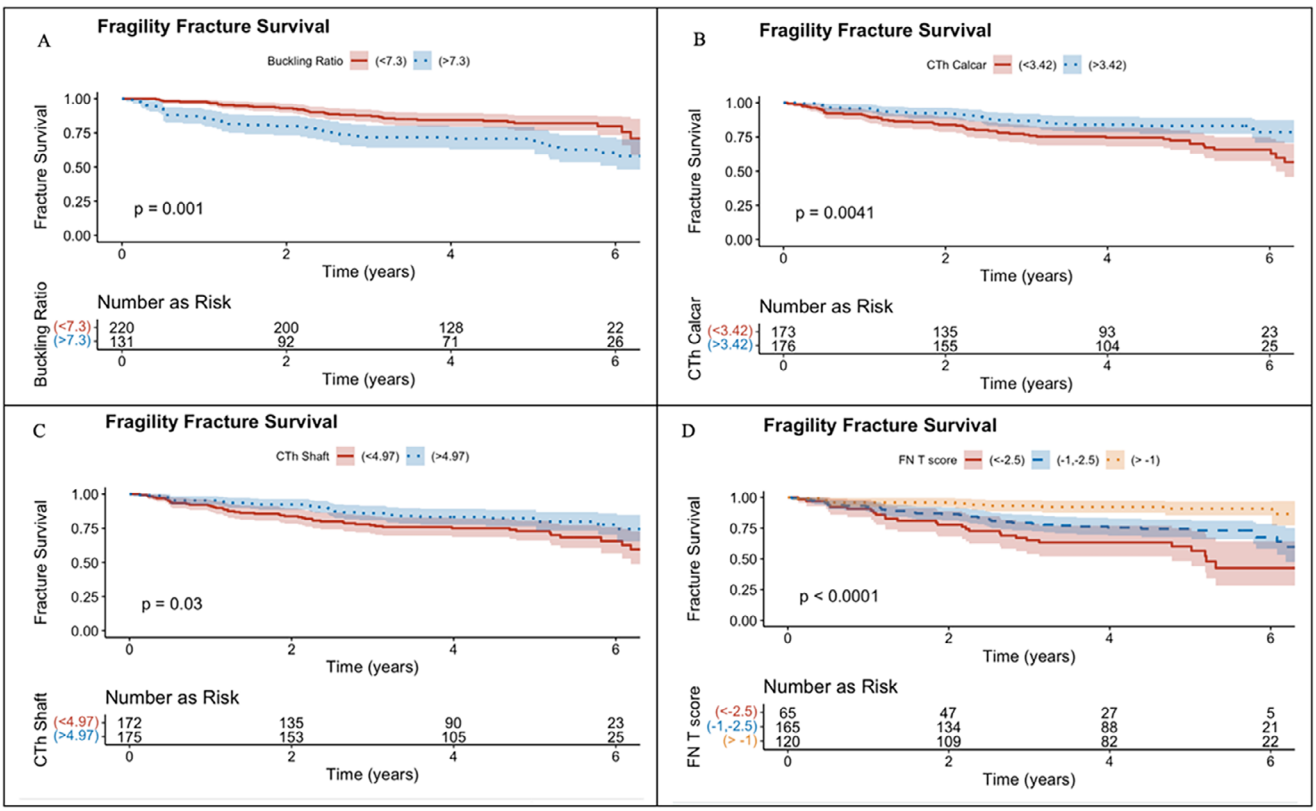


**FIGURE 2** | Fragility fracture survival after kidney transplant comparing (A) buckling ratio, (B) cortical thickness (CTh) calcar, (C) CTh shaft, and (D) femoral neck (FN) *T* score, unadjusted.

**TABLE 3** | Univariable and multivariable Cox proportional hazard model analyses for fragility fracture after kidney transplant.

| Characteristic | Univariable | | | | | Multivariable Model 1 AIC = 680 | | | | Multivariable Model 2 AIC = 714 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | Event *N* | HR[a] | 95% CI[a] | *p* value | Event *N* | HR[a] | 95% CI[a] | *p* value | Event *N* | HR[a] | 95% CI[a] | *p* value |
| Age at transplant (years) | 357 | 83 | 1.00 | 0.98, 1.01 | 0.7 | | | | | | | | |
| Gender | 357 | 83 | | | >0.9 | | | | | | | | |
| Female | | | — | — | | | | | | | | | |
| Male | | | 1.00 | 0.65, 1.56 | | | | | | | | | |
| BMI (kg/m$^2$) | 338 | 79 | | | 0.3 | | | | | | | | |
| (0,18) | | | — | — | | | | | | | | | |
| (18,25) | | | 0.88 | 0.21, 3.71 | | | | | | | | | |
| (25,30) | | | 0.53 | 0.12, 2.27 | | | | | | | | | |
| (30,60) | | | 0.70 | 0.17, 2.94 | | | | | | | | | |
| Dialysis vintage (months) | 308 | 74 | | | 0.13 | 68 | | | 0.6 | 71 | | | 0.2 |
| (0,60) | | | — | — | | | — | — | | | — | — | |
| (> 60) | | | 0.61 | 0.32, 1.20 | | | 0.79 | 0.36, 1.74 | | | 0.64 | 0.30, 1.37 | |
| Smoking status (non, former or current) | 339 | 77 | | | 0.006 | 68 | | | 0.028 | 71 | | | 0.020 |
| No | | | — | — | | | — | — | | | — | — | |
| Yes | | | 1.89 | 1.20, 2.97 | | | 1.75 | 1.06, 2.91 | | | 1.77 | 1.09, 2.87 | |
| T1DM | 347 | 83 | | | <0.001 | 68 | | | 0.001 | 71 | | | 0.012 |
| No | | | — | — | | | — | — | | | — | — | |
| Yes | | | 3.26 | 2.10, 5.06 | | | 2.50 | 1.43, 4.36 | | | 1.98 | 1.18, 3.32 | |
| T2DM | 345 | 81 | | | 0.5 | | | | | | | | |
| No | | | — | — | | | | | | | | | |
| Yes | | | 0.83 | 0.46, 1.50 | | | | | | | | | |
| Glucocorticoid use for > 3 months pre-transplant | 338 | 79 | | | 0.7 | | | | | | | | |
| No | | | — | — | | | | | | | | | |
| Yes | | | 1.14 | 0.66, 1.97 | | | | | | | | | |
| Prevalent fracture status | 341 | 81 | | | 0.070 | 68 | | | 0.6 | 71 | | | 0.7 |
| No | | | — | — | | | — | — | | | — | — | |
| Yes | | | 1.50 | 0.97, 2.33 | | | 1.15 | 0.70, 1.89 | | | 1.10 | 0.68, 1.78 | |

(Continues)

**TABLE 3** | (Continued)

| Characteristic | Univariable | | | | | Multivariable Model 1 AIC = 680 | | | | Multivariable Model 2 AIC = 714 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | Event *N* | HR[a] | 95% CI[a] | *p* value | Event *N* | HR[a] | 95% CI[a] | *p* value | Event *N* | HR[a] | 95% CI[a] | *p* value |
| Serum 25-hydroxy-vitamin D | 331 | 81 | | | 0.003 | 68 | | | 0.041 | 71 | | | 0.041 |
| < 50 nmol/L | | | 2.01 | 1.29, 3.14 | | | — | — | | | — | — | |
| > 50 nmol/L | | | — | — | | | 1.76 | 1.04, 2.98 | | | 1.71 | 1.03, 2.84 | |
| PTH (ref range 2.0–9.3) | 345 | 83 | | | 0.5 | | | | | | | | |
| <21 pmol/L | | | — | — | | | | | | | | | |
| (21–63 pmol/L) | | | 1.35 | 0.76, 2.39 | | | | | | | | | |
| >63 pmol/L | | | 1.08 | 0.59, 1.97 | | | | | | | | | |
| ALP | 356 | 83 | | | 0.063 | | | | | | | | |
| <110 U/L | | | — | — | | | | | | | | | |
| >110 U/L | | | 1.52 | 0.98, 2.34 | | | | | | | | | |
| Buckling ratio | 352 | 82 | 1.05 | 1.01, 1.08 | 0.016 | 68 | 0.96 | 0.91, 1.01 | 0.082 | | | | |
| Cortical thickness femoral neck | 352 | 82 | 1.11 | 0.99, 1.25 | 0.057 | | | | | | | | |
| Cortical thickness calcar | 351 | 82 | 1.35 | 1.08, 1.66 | 0.005 | | | | | | | | |
| Cortical thickness shaft | 350 | 82 | 1.17 | 1.02, 1.36 | 0.023 | | | | | | | | |
| Trabecular bone score | 351 | 80 | 5.55 | 1.03, 33.3 | 0.047 | 68 | 1.02 | 0.097, 11.1 | >0.9 | | | | |
| Femoral neck *T*-score | 350 | 83 | 1.72 | 1.38, 2.12 | <0.001 | 68 | 1.63 | 1.19, 2.27 | 0.002 | 71 | 1.49 | 1.11, 2 | 0.006 |
| Lumbar spine *T*-score | 351 | 82 | 1.20 | 1.04, 1.36 | 0.008 | 68 | 1.01 | 0.81, 1.25 | >0.9 | 71 | 1.03 | 0.85, 1.23 | 0.8 |
| Total proximal femur *T*-score | 350 | 83 | 1.56 | 1.31, 1.88 | <0.001 | | | | | | | | |
| Ultra-distal radius *T*-score | 243 | 66 | 1.21 | 1.06–1.40 | 0.004 | | | | | | | | |
| One-third radius *T*-score | 243 | 66 | 1.03 | 0.83, 1.28 | 0.8 | | | | | | | | |

*Notes:* Cortical width shaft, neck and calcar, total proximal femur and radial parameters were excluded due to collinearity in the Multivariable model. Models 1 and 2 compared goodness of fit by AIC. Model 1 included buckling ratio and the TBS, these novel parameters were excluded in model 2.

Abbreviations: AIC, Akaike information criterion; ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; HR, hazard ratio; *N*, number; PTH, parathyroid hormone; TBS, trabecular bone score, T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; 95% CI, 95% confidence interval.

[a]HR, hazard ratio.

patients with CKD, KF requiring dialysis [10, 21, 22] and in kidney transplant recipients [7, 12, 23].

After adjustment, excluding several BMD and cortical parameters due to collinearity, the TBS, remaining AHA parameters, and lumbar spine *T*-scores were no longer significantly associated with fracture, whereas the femoral neck *T*-score remained significant. An association of fracture with *T*-scores at the hip, but not at the lumbar spine has been observed in other studies [5, 24]. Possible explanations include the common occurrence of lumbar spine artefact due to degenerative changes, aortic calcifications, differing effects of PTH on trabecular and cortical bone, and study power. The CV for BMD at the lumbar spine and femur is typically better than 1% using the iDXA densitometer, and 1.5%–2% for the TBS, whereas the CV for AHA is 5%–7%, depending on orientation. This may have contributed to the stronger association of fracture outcomes with femoral BMD rather than AHA parameters in multivariable analyses.

We included fractures of the hand and foot because these sites are rich in cortical bone, which is disproportionately affected in patients with CKD and leads to a greater susceptibility to fractures at those sites. The effect of bisphosphonates on cortical bone remains questionable [25], and with long-term use, an increase in cortical crystallinity, mineral matrix ratio, and microhardness [26] may even contribute to fracture risk. However, in patients with CKD, with altered bone remodeling and increased cortical porosity, the effect of bisphosphonates requires further investigation.

This study highlights the extreme risk of post-transplant fracture in patients with T1DM. Whereas the post-transplant fracture incidence was 39/1000 patient years for KO recipients, which is similar to previous studies [7], the fracture incidence for patients with T1DM was 147/1000 patient years. Furthermore, 40% of the cohort's fractures occurred in the 20% of patients with T1DM, while 60% occurred in the 80% with KF from other causes. The immunosuppressive protocol followed for both KO and SPK transplants included glucocorticoid minimization but not withdrawal. While there is a paucity of data on corticosteroid withdrawal following SPK transplantation, a recent retrospective study reported that to 10-years post-transplant there were no differences in pancreas or kidney allograft survival, or immunologic allograft loss, for patients undergoing early steroid withdrawal versus chronic corticosteroid immunosuppression [27]. The current study underscores the need to consider both preemptive management and alternative post-transplant treatments that may reduce fracture risk in these vulnerable patients.

Patients with KF from T1DM have changes in high-resolution peripheral quantitative computed tomography associated with poor bone quality [28]. T1DM impacts bone due to the effect of hyperglycemia and advanced glycation end products on collagen cross-linking, and the suppression of osteoblastic differentiation and mineralization [29]. Additionally, insulin and insulin-like growth factors have anabolic roles in bone metabolism, and deficiency of these hormones during childhood retards the attainment of peak bone mass [28, 30, 31]. Microvascular pathology may also predispose to fracture in patients with T1DM, with mechanisms including an increase in cortical porosity and reduced cortical strength. In a large Swedish study, the risk of hip fracture was increased 17- to 41-fold in patients with T1DM and microvascular disease, versus 3- to 6-fold when microvascular disease was absent [32].

In addition to T1DM, prior smoking and serum 25-hydroxyvitamin D values < 50 nmol/L were risk factors for post-transplant fracture, and these, in addition to femoral neck *T*-scores, remained associated with incident fracture after adjustment for other variables. Although there is no high-level evidence to support pre-transplant repletion of vitamin D, a single-center study reported higher 25-hydroxyvitamin D values at the time of transplantation, and post-transplant cholecalciferol supplementation was associated with lower fracture rates over 12-months [33]. Microvascular pathology is likely to also be exacerbated by tobacco consumption, and it is plausible that in this study, smoking-related microvascular changes may have increased fracture risk when superimposed on those of CKD and T1DM.

In this study, transplant recipients were selected for antiresorptive therapy based on an algorithm to reduce loss of BMD [19], with patients at highest risk, based predominantly on lower BMD *T*-scores, and with normal or elevated bone turnover after transplantation, generally allocated to treatment with an oral bisphosphonate. This is unlikely to compromise the outcomes of this study, because if bisphosphonate treatment is effective, the association between fracture and lower BMD, or abnormal AHA parameters, would be attenuated, suggesting that the association may be more robust than we have reported. Compared to lower-risk patients not allocated to bisphosphonate therapy, patients at high fracture risk and treated with antiresorptive therapy had a significant increase in BMD at both the lumbar spine and hip, and a non-significant increase in TBS over 12 months. These patients also had higher incident fractures, because allocation to antiresorptive therapy is a surrogate for fracture risk, as documented in the general population [34] and within a kidney transplant cohort [24]. In other post-kidney transplant studies, the efficacy of bisphosphonates for improving BMD remains uncertain, and a Cochrane review of 13 small RCTs showed heterogeneity in treatment effect [35]. Overall, the current results support the use of the fracture risk algorithm to identify high-risk patients and support the efficacy of bisphosphonates to maintain or improve BMD in selected patients. Nevertheless, an adequately designed randomized controlled trial is necessary to confirm these findings, and it remains possible that patients with normal or high bone turnover may have greater "spontaneous" post-transplant BMD recovery. AHA parameters and the TBS were not included in the risk/management algorithm that was used, but when BRs above or below median values were included as an additional step, this further improved fracture prediction after adjustment for all other significant covariates.

This study has several strengths and some limitations. Strengths include that patients were followed prospectively, with pre-transplant laboratory data, immediate post-transplant DXA, and carefully adjudicated fracture identification. Patient outcomes were assessed using local records and access to the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), so that the only loss to follow-up was when patients transferred to another health district, leading to fracture data no longer being available. Limitations include that only symptomatic vertebral

fracture data was collected from the PAH cohort, which will have resulted in a probable underestimation of total fracture events, and forearm BMD data was incomplete. Additionally, patients considered to have the highest fracture risk received treatment at WH according to an algorithm that may have influenced fracture outcomes, while management was similar, but less protocol driven, at the PA site. It is possible that non-significant associations of TBS, AHA, and fracture in multivariate analyses may have differed in a treatment-naïve population. The observation that baseline femoral neck BMD is associated with fracture risk despite treatment interventions emphasizes its robustness as a risk biomarker. We did not find that gender, BMI, or ethnicity was associated with fracture outcomes in this relatively young patient population, which was predominantly Caucasian and Asian (including South and South-East Asian), with only a few Australian Aboriginal individuals and Pacific Islanders, and even fewer African or Afro-American patients who may have had a reduced fracture risk. Therefore, results may differ in patient groups that are older, or of different ethnicity.

## 5 | Conclusion

Our study has demonstrated that fracture incidence is high after transplantation, particularly among patients with T1DM. Additional risk factors include prior smoking and low 25-hydroxyvitamin D values, which remain significantly associated with fracture after multivariable adjustment and might be modified pre-transplant. BMD *T*-scores at the femur and spine, the TBS and AHA parameters, are also associated with post-transplant fracture, and after adjustment, femoral neck BMD remained significant. This suggests that interventions to improve BMD in the pre-transplant period may affect post-transplant fracture risk and supports the concept that for patients with KF, "CKD-associated bone fragility" or "CKD-associated osteoporosis" might be considered as treatment targets. The treatment algorithm used in this study was also shown to identify patients with a high fracture risk. High-risk patients treated with antiresorptive therapy showed stable or improved BMD within 12 months, whereas those considered low risk for BMD loss and fracture, who did not receive antiresorptive treatment, had stable or declining BMD. When an interaction term for BRs above or below the median was added to the management algorithm, this reclassified some patients predicted to have low fracture risk to a higher fracture risk category, which could inform treatment allocation. Importantly, this study identifies risk factors that are amenable to pre-transplant modification and highlights the characteristics of patients at high risk of fracture, who might benefit from effective therapeutic interventions.

### Author Contributions

All authors worked on the design of the study. Tahira Scott and Grahame J. Elder analyzed the data, constructed figures, and drafted the paper. Mirna Vucak-Dzumhur, Jasna Aleksova, Harpreet Kaur, Mina Khair, Ryan Gately, Carmel Hawley, Christopher Schultz, James Elhindi, and Grahame J. Elder provided guidance on data analysis and interpretation. Ryan Gately and James Elhindi provided statistical advice. Tahira Scott and Grahame J. Elder revised the paper with input from other authors, and all authors read and approved the final manuscript.

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### Conflicts of Interest

C.H. reports personal fees from GlaxoSmithKline and grant support from Baxter, Fresenius, and NHMRC, outside the submitted work. The remaining authors have no relevant disclosures. There are no conflicts of interest.

### Data Availability Statement

Deidentified data from the Brisbane and the Westmead sites were combined for analysis in this study. The authors will perform further analyses in response to any reasonable request sent to the senior author (Prof. Grahame Elder). The authors are not permitted to release deidentified patient data without approval by the Human Research Ethics Committees (HRECs) at both sites. However, HREC permission will be sought upon receipt of any reasonable request for data access.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.