Change in Patellar Cartilage from 2.5 to 4.5 Years Following ACL Reconstruction With and Without Meniscal Pathology

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Abstract

Background: Anterior cruciate ligament reconstruction (ACLR) together with concomitant meniscal injury are risk factors for the development of tibiofemoral (TF) osteoarthritis (OA), but the potential effect on the patellofemoral (PF) joint is unclear. The aim of this study was to: (i) investigate change in patellar cartilage morphology in individuals 2.5 to 4.5 years after ACLR with or without concomitant meniscal pathology and in healthy controls, and (ii) examine the association between baseline patellar cartilage defects and patellar cartilage volume change.

Methods: 32 isolated ACLR participants, 25 ACLR participants with combined meniscal pathology and nine healthy controls underwent knee magnetic resonance imaging (MRI) with 2-year intervals (baseline = 2.5 years post-ACLR). Patellar cartilage volume and cartilage defects were assessed from MRI using validated methods.

Results: Both ACLR groups showed patellar cartilage volume increased over 2 years ($p < 0.05$), and isolated ACLR group had greater annual percentage cartilage volume increase compared with controls (mean difference 3.6%, 95% confidence interval (CI) 1.0%, 6.3%, $p = 0.008$) and combined ACLR group (mean difference 2.2%, 95% CI 0.2%, 4.2%, $p = 0.028$). Patellar cartilage defects regressed in the isolated ACLR group over 2 years ($p = 0.02$). Baseline patellar cartilage defect score was positively associated with annual percentage cartilage volume increase (B = 0.02; 95% CI 0.003, 0.03; $p = 0.02$) in the pooled ACLR participants.

Conclusions: Hypertrophic response was evident in the patellar cartilage of ACLR participants with and without meniscal pathology. Surprisingly, the increase in patellar cartilage volume was more pronounced in those with isolated ACLR. Although cartilage defects stabilise in the majority of ACLR participants, the severity of patellar cartilage defects at baseline influenced the magnitude of the cartilage hypertrophic response over the subsequent ~2 years.

Background

Anterior cruciate ligament reconstruction (ACLR) is a common treatment following ACL injury. Whilst ACLR is typically effective in restoring anterior knee stability, a substantial portion of ACLR patients will develop early onset knee osteoarthritis (OA) – a painful and debilitating condition for which there is no known cure [1–4]. Traditionally, research has focused on tibiofemoral (TF) joint OA following ACLR; however, a high prevalence of OA in the patellofemoral (PF) joint following ACLR has been reported [5, 6] and which is characterised by knee symptoms such as pain and reduced function [5].

Meniscal injury frequently occurs at the time of the ACL injury and has been recognised as a risk factor for knee OA [1, 7, 8]. Biomechanical changes following meniscal injury or resection are thought to influence anterior-posterior laxity of the PF joint and internal-external rotation of the TF joint [9, 10]; thus, altered PF and TF joint biomechanics likely predispose the knee joint to OA development [11]. A previous study [5] reported that medial meniscal injury increased the risk of developing PF joint OA and medial TF

joint OA at 5–10 years post-ACLR. A prospective evaluation of PF cartilage changes in ACLR knees with and without concomitant meniscal injury is warranted to understand PF joint OA cartilage pathophysiology.

Magnetic resonance imaging (MRI) is a non-invasive method to assess knee cartilage morphology with demonstrated sensitivity and reliability [12]. MRI studies have revealed alterations in cartilage morphology in the early years following ACL injury and ACLR [13, 14]. Morphological changes vary according to the knee compartment as both cartilage increases and decreases have been reported at 1–5 years post-surgery [15–18]. In particular, a longitudinal study demonstrated a general increase in TF joint cartilage thickness over a 5-year post-operative period [15], suggesting a alteration of cartilage homeostasis [15] prior to cartilage breakdown [15–17]. By contrast, a recent study reported a decreased in total PF joint cartilage thickness over 5 years following ACL injury [14]. Cartilage defects, a MRI-derived semi-quantitative cartilage morphology measurement, indicate early pathology following joint injury [18, 19]. Potter et al. [20] reported progressive worsening of patella cartilage defects following ACL injury over 11 years regardless of treatment (i.e., ACLR or conservative management). These findings demonstrated PF joint cartilage loss and degeneration following ACL injury/ACLR. In addition, the detrimental long-term effects of cartilage defects have been established in the TF joint. Whilst severe baseline cartilage defects were associated with cartilage loss in knee OA populations [21, 22], we found that mild baseline cartilage defects were associated with greater increases in cartilage volume in an ACLR cohort [23]. Thus, it is of interest to examine whether baseline cartilage defects are associated with changes in patella cartilage morphology following ACLR.

The aims of this study were twofold. The first aim was to investigate the changes of patellar cartilage volume and cartilage defects from 2.5 to 4.5 years after ACLR in participants with: i) isolated ACLR without meniscal pathology, ii) ACLR combined with meniscal pathology, and (iii) healthy controls. It was hypothesised that: H_1): ACLR knees would show increased patellar cartilage volume and increased cartilage defects score (progression), whilst control knees would show no change over 2-year; H_2): knees with combined ACLR and meniscal pathology would show greater increase in cartilage volume and greater increase in cartilage defect scores compared with ACLR isolated knees. The second aim was to examine the association between baseline patellar cartilage defects scores and cartilage volume change in ACLR knees. It was hypothesised that: H_3): higher cartilage defects at baseline would be associated with greater cartilage volume increase after 2 years.

Methods

Participants

One hundred participants who had undergone ACLR were recruited in Melbourne (Epworth Hospital Richmond) and Gold Coast (Pindara Hospital, Pacific Private Hospital, and John Flynn Hospital) Australia. ACLR participants were included based on the following criteria: (i) aged 18–40 years; (ii) ACLR performed within 6 months of injury; (iii) baseline assessments were performed at 2–3 years post-

surgery; and (iv) ACLR was performed using the semitendinosus and gracilis autograft [23]. Exclusion criteria included: (i) evidence of tibiofemoral OA (International Cartilage Repair Society (ICRS) cartilage defects grade > 2 or osteophytes on arthroscopy or X-ray at the time of recruitment); (ii) additional musculoskeletal, cardiovascular, or neurological conditions; (iii) previous ACL rupture or subsequent knee surgery on the involved leg; (iv) body mass index (BMI) > 34 kg/m^2, or (v) any physician recommendations against undergoing MRI [24]. Eligible participants who had concomitant meniscal pathology (i.e., meniscal injury, repair or partial meniscectomy) at the time of ACLR were categorized to the combined ACLR and meniscal pathology group. Thirty healthy individuals without history of knee injury and lower-limb surgery were recruited as controls from the local university community. Control participants were age and BMI matched to ACLR participants (i.e., 18–40 years and BMI < 34 kg/m^2).

ACLR surgery was arthroscopically assisted, and tibial and femoral tunnels were drilled using a 4.5 mm gauge drill. A notchplasty was performed as required to ensure that graft impingement did not occur. A four-strand autograft was created by semitendinosus and gracilis tendons which were harvested through a 3–4 cm incision over the pes anserinus. Tibial fixation was achieved with an interference screw, while femoral fixation used an appropriately sized Closed Loop Endobutton (Smith and Nephew Endoscopy, MA, USA). The management of the meniscal injury (i.e., leave as is, repair, or partial meniscectomy) was determined by the surgeon based on the injury appearance at the time of surgery. Meniscal repair was performed when the surgeon judged the lesion repairable. Partial meniscectomy was performed for non-repairable meniscal injuries that were considered to be potentially symptomatic. No chondral surgery was performed as all lesions were not considered serious (ICRS score grade < 3). Patients were discharged from hospital on the first postoperative day and weight bearing on the involved knee was encouraged on an as-tolerated basis without the use of braces or splints. The ACLR rehabilitation protocol targeted on rapid restoration of knee range of motion as well as quadriceps function.

Anthropometry

Mass and height were measured, and then used to calculate BMI (kg/m^2).

Magnetic resonance imaging

The MRI protocol and assessment have been presented previously [24] and are briefly summarized below. The MRI scans were performed at baseline (i.e., 2–3 years post-ACLR) and at follow-up 2 years later using whole-body MRI units in Melbourne (3.0 T, Siemens Magenetom Verio, Erlangen, Germany) and the Gold Coast (1.5 T, GE Healthcare Signa, Wisconsin, USA). Knees were imaged using T_1-weighted 3-dimensional gradient recall sequences in the sagittal plane [25].

Patella cartilage volume and patella bone volume

Patella cartilage volume was measured based on the T_1-weighted images using a previously published method [24, 25]. Images were transferred to Osiris v4.19 software (University Hospital of Geneva, Geneva, Switzerland) and cartilage was manually segmented by tracing the osteochondral interface and articular surface slice-by-slice. Cartilage volume (mm^3) was determined by summing segmented areas and

multiplying by slice thickness (1.5 mm). Baseline and follow-up cartilage volumes were measured in pairs for each participant by one trained assessor (XW) who was blinded to participant status. Intra-class correlation coefficients (ICC) for intra-rater and inter-rater reliability were 0.997 and 0.993, respectively [24]. Baseline patella bone volume was measured for statistical adjustment using the same method as for cartilage volume with ICCs above 0.98. The annual percentage change in patella cartilage volume was calculated as follows: (follow-up patella cartilage volume minus baseline patella cartilage volume) divided by (baseline patella cartilage volume multiplied by time period between scans). Positive values indicate increased cartilage volume over time.

Cartilage defects

Cartilage defects were assessed in T_1-weighted images using the ICRS cartilage defect grade (score 0–4) as previously described [18, 24, 26]. Intra-observer and inter-observer reliability, expressed as ICCs, were 0.94 and 0.93, respectively [24]. Cartilage defects were considered to have: 1) 'progressed' if defect grade increased (i.e., worsened), 2) 'regressed' if the defect grade decreased (i.e., improved), or 3) 'stable' if defect grade did not change over 2 years.

Statistical analysis

Mean ± standard deviation was calculated for parametric variables, and changes over time were assessed using paired samples T-tests. Median ± interquartile range was calculated for non-parametric variables, and changes over time were assessed using Wilcoxon signed-rank tests. Participant characteristics were compared using independent samples T-tests or Chi-squared tests. Group-differences in annual percentage change in cartilage volume were compared using an analysis of covariance (ANCOVA) adjusting for the covariates of age, gender, BMI, baseline cartilage defect grade, and baseline patella bone volume. To explore between group differences in cartilage defect changes (i.e., progression and regression), Chi-squared and Fisher's exact tests were used. If significant main effects were identified, *post hoc* comparisons were performed using Fisher's least significant difference (LSD). Univariate and multivariate linear regression was used to examine the relationship between baseline cartilage defects and cartilage volume change in all ACLR participants before and after adjusting for age, gender, BMI, baseline patella bone volume, and presence of meniscal pathology. All statistical analyses were performed in SPSS (IBM, Chicago, USA) version 24.0 with significance set to $p < 0.05$.

Results

As per our previous study [23], 66 participants returned for follow-up assessments (32 ACLR isolated, 25 ACLR combined, and 9 controls) and the characteristics of the three groups are shown in Table 1. The ACLR combined group exhibited a higher BMI than the ACLR isolated group ($p = 0.007$). The control group had a longer follow-up time interval between MRI assessments compared to both ACLR groups ($p < 0.001$).

Table 1
Characteristics of participants.

	ACLR isolated (n = 32)	ACLR combined (n = 25)	Controls (n = 9)	*p* value
Age (yrs)	30.7 (± 6.4)	30.6 (± 7.1)	28.3 (± 4.0)	0.58
Male, n (%)	19 (59)	18 (72)	8 (89)	0.24
BMI (kg/m^2)	24.4 (± 3.2)[1]	27.0 (± 3.6) [1]	24.6 (± 3.8)	0.02*
Time from surgery to baseline (yrs)	2.5 (± 0.4)	2.5 (± 0.4)	Not applicable	0.92
Time from baseline to follow-up MRI (yrs)	2.1 (± 0.2) [2]	2.0 (± 0.2) [3]	2.9 (± 0.4) [2 3]	< 0.001*
Parametric data are presented as mean (± standard deviation). ACLR: anterior cruciate ligament reconstruction; BMI, body mass index; MRI, magenetic resonance imaging.				
*Significant difference ($p < 0.05$). *Post hoc* was significantly different for [1] isolated ACLR versus combined ACLR, [2] isolated ACLR versus controls, [3] combined ACLR group versus controls.				

Reasons for drop-out have also been previously reported [23] and included: 21 uncontactable, 11 time commitment, 5 subsequent ACL or meniscal injury, 2 MRI scanner issues, 3 pregnancy or wearing intrauterine device (IUD), and 22 relocation. Characteristics of participants who completed follow-up assessment and those who did not were similar, showing no significant difference in ACLR participants (Additional file Table A1) and control participants (Table A2).

Within-group Comparisons

Cartilage volume

ACLR groups exhibited a positive patellar cartilage volume change ($p < 0.05$, Table 2), while the control group showed no significant change during the follow-up period.

Table 2
Baseline and follow-up patellar cartilage volume, cartilage volume change, and adjusted annual percentage change.

	ACLR isolated (n = 32)	ACLR combined (n = 25)	Controls (n = 9)	*p* value
Baseline cartilage volume (mm^3)	3328 (822)	3470 (555)	3830 (836)	0.20
Follow-up cartilage volume (mm^3)	3548 (854)	3596 (634)	3839 (937)	0.62
Patellar cartilage volume change (mm^3)	220 (139, 301)[1 a]	126 (26, 226) [a]	9 (-165, 183)[1]	0.046*
Annual percentage change in patellar cartilage volume (%)[#]	3.5 (2.3, 4.8)[1 2]	1.3 (-0.1, 2.8)[2]	-0.1 (-2.5, 2.3)[1]	0.01*

Baseline and follow-up patellar cartilage volume were presented as mean (SD). Patellar cartilage volume change and annual percentage change in patellar cartilage volume are presented as mean (95% confidence interval). Patellar cartilage volume change = follow-up volume - baseline volume, thus positive values represent an increase in cartilage volume. *Significant difference ($p < 0.05$). [#]Adjusted for age, gender, BMI, baseline cartilage defect score, and baseline patellar bone volume. *Post hoc* was significantly different for [1] isolated ACLR versus controls, [2] isolated ACLR versus combined ACLR, [a] follow-up versus baseline.

Cartilage defects

ACLR isolated group showed a decrease in patellar cartilage defect scores ($p = 0.02$; see Table A3).

Between-group Comparisons

Cartilage volume

ACLR isolated group had greater annual percentage change in cartilage volume than the control group ($p = 0.008$, mean difference 3.6%, 95% confidence interval (CI) 1.0%, 6.3%) and ACLR combined group ($p = 0.028$, mean difference 2.2%, 95% CI 0.2%, 4.2%). However, no significant differences were found between ACLR combined and control groups (Table 2).

Cartilage defects

Most participants in each group had stable cartilage defects (Table 3). Although ACLR groups showed cartilage defect regression in a quarter of participants (25% of ACLR isolated and 24% of ACLR combined), no significant difference was found.

Table 3
Patellar cartilage defects change in each group given as number (%).

	ACLR isolated (n = 32)	ACLR combined (n = 25)	Controls (n = 9)	*p* value
Baseline defect score				0.26
Grade 0	18 (56%)	15 (60%)	7 (78%)	
Grade 1	12 (38%)	7 (28%)	1 (11%)	
Grade 2	1 (3%)	3 (12%)	0 (0)	
Grade 3	1 (3%)	0 (0)	0 (0)	
Grade 4	0 (0)	0 (0)	1 (11%)	
Follow-up defect score				0.42
Grade 0	25 (78%)	20 (80%)	7 (78%)	
Grade 1	5 (16%)	2 (8%)	1 (11%)	
Grade 2	1 (3%)	3 (12%)	0 (0)	
Grade 3	1 (3%)	0 (0)	0 (0)	
Grade 4	0 (0)	0 (0)	1 (11%)	
Defect changes				
Progression	1 (3%)	2 (8%)	0 (0)	0.73
Stable	23 (72%)	17 (68%)	9 (100%)	0.18
Regression	8 (25%)	6 (24%)	0 (0)	0.29

Associations between baseline cartilage defects and annual percentage patellar cartilage volume change in ACLR groups

Among ACLR participants, the association between baseline cartilage defect and annual percentage patellar cartilage volume change was found before ($p = 0.04$) and after adjustment ($p = 0.02$). After adjustment for potential confounders, the increase in patellar cartilage volume were positively associated with higher baseline patella cartilage defects scores (regression coefficient (B) 0.02; 95% CI 0.003, 0.03; R2 = 0.44; Beta = 0.33).

Discussion

This longitudinal study examined changes in patellar cartilage morphologic features (i.e., cartilage volume and cartilage defects) in ACLR knees with or without combined meniscal pathology from 2.5 to

4.5 years post-surgery, as well as a control group assessed over 2 years. ACLR groups demonstrated an increase in patella cartilage volume whilst control participants exhibited no change over the study period. Moreover, the isolated ACLR group showed a higher level of patella cartilage volume increase than the combined ACLR and control groups. Patellar cartilage defect scores significantly regressed in the isolated ACLR group. Finally, baseline patellar cartilage defect scores were positively associated with the increase in patellar cartilage volume over 2 years in ACLR participants.

Consistent with H_1, both isolated and combined ACLR knees showed significant increases in patellar cartilage volume at follow-up compared to baseline, while the patellar cartilage volume of the control group exhibited no significant change. Increase in patellar cartilage volume in ACLR knees is consistent with results of several recent longitudinal studies that have also reported increased knee cartilage volume or thickness within 1–5 years post-ACLR [15–17, 23] - albeit in the TF joint compartments. These findings may be indicative of early OA development that where cartilage increases have been reported prior to cartilage loss and may be due to tissue hypertrophy, repair and swelling [15]. In contrast to the current study, Culvenor et al. [14] reported decreased PF cartilage thickness at 5-years following ACLR- a finding which, given the follow-up period, may be reflective of a more advanced stage of cartilage degeneration than the current study. In the early stages of cartilage degeneration, cartilage increase is suggestive of accelerated metabolism and increased water - an adaptive response to repair cartilage damage and withstanding mechanical load [27, 28]. Whilst identifying the biomechanical mechanisms contributing to patella cartilage increase are beyond the scope of this study, PFJ '*underloading*' during running in a comparable cohort of ACLR patients has been reported [29]. Decreased PFJ loading has been associated with early degenerative changes in ACL-transected animals [30, 31]. In humans, a relationship between TF joint underloading and the development of early-onset TF osteoarthritis has been identified [32]. Clearly, the definitive biomechanical conditions that contribute to the pathogenesis of PFJ OA post-ACLR need to be the focus of future studies.

In contrast to H_2, ACLR isolated knees exhibited a greater increase in annual percentage change in patella cartilage volume than the combined ACLR and control knees. Meniscectomy and meniscal injuries have been associated with a higher prevalence of TF and PF joint OA following ACLR [7, 33, 34]. For this reason, we hypothesised (H_2) that combined ACLR knees would demonstrate more pronounced cartilage volume change compared to isolated ACLR and control knees. However, our results indicate the opposite, and no differences were found between combined ACLR and control knees. This unexpected finding may be related to the fact that degenerative changes occur across cartilage sub-regions at different rates. In this respect, Eckstein et al.[15] whilst adopting a different technique for quantifying cartilage morphology, reported concurrent TF cartilage thickening and thinning in different sub-regions within the same cartilage compartment in post-ACLR participants. It has been widely accepted that an increase in cartilage volume precedes cartilage thinning during the process of cartilage degeneration [28]. Overall cartilage morphology is a direct result of the balance between cartilage hypertrophy and loss. The isolated ACLR group experienced greater patellar cartilage volume increase suggesting that, on balance, increasing cartilage volume was the predominant change across the plate sub-regions. In contrast,

combined ACLR knees may have been undergoing a higher level of cartilage thinning in some sub-regions due to more rapid degeneration compared with isolated ACLR knees. This argument is also supported in the TF joint, as our previous research has demonstrated the same between-group difference in the lateral tibia [23].

Contrary to H_1, the majority of participants in each of the three groups had stable cartilage defects meaning defect grades were unchanged between baseline and follow up assessment time points. The stability of the cartilage defects in both ACLR groups suggests that the cartilage defects persist from 2.5–4.5 years post-ACLR. This notion is supported by Potter et al. (2012) who found cartilage defects in all 40 patients at the time of ACL injury, and minimal subsequent change in cartilage defect size until ~ 7 years post injury, at which point there was a marked increase in defect [20]. It is likely that the increase at this latter time represents acceleration of the degenerative processes, and is consistent with the higher rates of OA development observed around this time period (i.e., over 10 years) post-injury[2, 4].

Notably and contrary to H_1, patellar cartilage defect scores significantly regressed in the isolated ACLR group and 25% of knees exhibited improvements in PF cartilage defects from baseline to follow-up. These improvements seem to be independent of concurrent meniscal injury, as 24% of the combined ACLR knees also showed cartilage defect improvement. This finding is different from previous studies showing one-way progression of patellar cartilage defects from 2–11 years following ACLR [20, 35]. In support however, another study [36] demonstrated that in a relatively young (i.e., mean age of 45 years) cohort of 325 participants, largely without radiographic OA, 13% of participants showed improvement in patellar cartilage defects over two-year period [36]. Improvement in cartilage defects, due to cartilage synthesis or swelling, reflects an attempt to repair cartilage damage and withstand mechanical load [28]. The natural history of cartilage defects was also age-related. In older groups, improvement of cartilage defects appears to be less common. Specifically, in a study of 395 participants with mean age 62.7 years, 26% cartilage defects progressed at the patella over 3 years, with the majority of defects remaining stable, and defect improvement rarely occurring (~ 1% of participants) [37]. In another study of 86 healthy participants with a mean age of 57 years, approximately 36% had worsening in patellar cartilage defects, while approximately 18% improved over 2 years [38]. Moreover, a recent study reported that 17% of ACLR participants had cartilage defects or osteophytes in the PF joint and, as such, were categorised as exhibiting MRI-defined PF joint OA [6]. Although defining early OA is of great value [39], results of the current study suggest that the definition of early OA should be carefully selected. Specifically, using the presence of mild cartilage defects as a diagnostic criterion for early OA may be inappropriate in either research or clinical setting, considering the regression of cartilage defects in a substantial portion of ACLR patients.

Contrary to H_2, there were no differences in changes in cartilage defects between the three groups. This lack of difference between groups may be attributable to the small change in cartilage defects over the 2-years, and/or the relatively small sample size with a lack of power to detect statistical differences.

In support of H_3, higher baseline cartilage defect scores at the patella of ACLR participants were associated with greater patellar cartilage volume increases over the subsequent two years. The positive relationship indicates that mildly disturbed cartilage homeostasis (i.e., ICRS 1–2 cartilage defects) was associated with cartilage adaptation, which may be indicative of early cartilage degeneration. This positive association between cartilage defects and increases in cartilage volume are consistent with our previous finding in the lateral tibia [22]. It is important to note that ACLR participants in this study were different from those included in previous studies which reported that more severe cartilage defects (i.e., ICRS 3–4) were associated with an increased likelihood of developing radiographic OA [33] and worse patient-report outcomes [40–43].

This study has several strengths. First, this is the first study to compare the change in patellar cartilage morphology between ACLR participants with and without concomitant meniscal pathology. Second, in contrast to most other longitudinal studies, we included an age-matched control group for comparative purposes. By contrast, our study also has several limitations. Firstly, 49% of the participants were lost to follow-up. Importantly, no difference in participant characteristics were identified between those participants who remained in the study and those lost to follow-up. Also, the sample size was relatively small for the combined ACLR group and the control group, which could reduce the statistical power of the study [22].

Conclusion

Patellar cartilage hypertrophy, suggestive of altered cartilage homeostasis, was apparent in ACLR knees with and without concomitant meniscal pathology at ~ 4.5 years after surgery. However, it may be inferred that patellar cartilage degenerative changes occur at different rates given the more pronounced increase in patellar cartilage volume in the ACLR isolated group compared to the ACLR combined group. Interestingly, cartilage defects were stable in the majority of ACLR participants. The severity of patellar cartilage defects at baseline do however, influence the cartilage hypertrophic response over the subsequent ~ 2 years.

Abbreviations

ACL: anterior cruciate ligament; ACLR: anterior cruciate ligament reconstruction; ANCOVA: analysis of covariance; BMI: body mass index; CI: Confidence Interval; ICCs: Intra-class correlation coefficients; ICRS: International Cartilage Repair Society; IUD: Intrauterine device; LSD: least significant difference; MRI: magnetic resonance imaging; OA osteoarthritis; PF: patellofemoral; TF: tibiofemoral

Declarations

1. Ethics approval and consent to participate

All research studies have been performed according to the rules of the local ethics committee. The University of Melbourne and Griffith University Human Research Ethics Committees approved the study (0932864.3 and PES/36/10/HREC, respectively). Informed written consent was obtained from participants for research studies and presented data.

2. Consent for publication

Not applicable.

3. Availability of data and material

The datasets used and analysed in the current study are available from the corresponding author on reasonable request.

4. Competing interest

The authors have no competing interests.

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6. Authors' contributions

All authors were involved in revising it critically for intellectual content. Study conception and design: XW, ALB, KLB, YW, TVW, FMC, DGL. Provision of patients: JAF, CJV, TW, PG. Acquisition of the data: KF, DJS, XW, BAK. Analysis and interpretation of data: XW, YW, KLB, ALB, FMC. Draft of the paper: XW, BAK, ALB, DJS, KF. Revision of paper: XW, ALB. Obtaining of funding: ALB, KLB, TVW, FMC, DGL. Final approval of the article: all authors.

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