Systematic Review

Patient Age and Activity Level, Posterior Tibial Slope, and Use of Allograft Are Significant Risk Factors for Anterior Cruciate Ligament Reconstruction Failure: A Systematic Review

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Purpose: To assess the consistency of risk factor reporting for anterior cruciate ligament reconstruction (ACLR) failure after primary reconstruction, identify risk factors more frequently associated with ACLR failure, and help clinicians prevent reinjury in patients with risk factors for ACLR failure. **Methods:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to conduct a systematic review. Initial title and abstract screening yielded 561 studies, from which 76 studies were assessed for eligibility. Thirty-two full-text studies met the following inclusion criteria: (1) clinical studies of anterior cruciate ligament injuries; (2) patients undergoing ACLR; (3) clinical outcome data, including failure rate; (4) studies assessing preoperative risk factors for failure; and (5) manuscripts published within the past 6 years. These studies were subdivided into those that defined ACLR failure as revision surgery or graft failure. **Results:** Ten risk factors were included in the review for 22 studies defining ACLR failure as revision surgery. Eight risk factors were included in the review for 10 studies defining ACLR failure as graft failure. Posterior tibial slope (PTS) (80%, 4/5 studies), age (79%, 11/14 studies), and graft characteristics (71%, 5/7 studies) such as allograft versus bone−patellar tendon−bone autograft, high-dose radiation, and BioCleanse preparation technique were the most significant risk factors for revision ACLR. PTS (100%, 2/2 studies) and activity level (67%, 2/3 studies) were the most significant risk factors for graft failure. **Conclusions:** Age, PTS, use of allograft, and activity level are significant preoperative risk factors that should be considered when attempting to prevent reinjury in ACLR candidates. Studies investigating risk factors for ACLR failure often fail to control for confounding variables that can influence outcomes. **Level of Evidence:** Level IV, systematic review of Level II to IV studies,

Anterior cruciate ligament (ACL) rupture is one of the most common orthopaedic injuries in the young adult population, with a predicted incidence of 69 per 100,000 person-years and rising in the United States.[1] ACL reconstruction (ACLR) restores knee stability and allows athletes to return to sport.[2] It also has the proposed benefit of reducing the risk of subsequent long-term chondral and meniscal damage.[3] At 10 years postoperatively, the risk of ACLR graft rupture is 7.9%, with prospective studies reporting a range of 3.2% to 11.1%, although the true value may be even higher.[1,4] The subsequent rate of revision ACLR procedures is between 2.9% and 5.8% in the literature.[5] Given the risks associated with chronic ACL deficiency, numerous clinical investigations have been performed to elucidate risk factors associated with ACLR failure following primary reconstruction.

The current body of literature has investigated the significance of a multitude of both preoperative and postoperative risk factors for ACLR failure. These include modifiable factors such as body mass index (BMI), graft selection/placement/fixation, posterior slope of the lateral or medial tibial plateau (LPTS/MPTS), activity level, time to surgery, and smoking.

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These also include nonmodifiable factors, including patient age, sex, height, race, and concomitant knee injuries.[6-13] Despite the exhaustive literature on ACLR failure, there remains disagreement on which factors are the most impactful risk factors.[9,11,12,14-18] These discrepancies can be partially attributed to methodologic differences in controlling and reporting confounding preoperative variables. Additionally, a plethora of intraoperative techniques vary between studies and surgeons and are often inadequately reported in the methods. This, in turn, has led to inconsistencies in identifying risk factors for ACLR failure and leaves surgeons with scarce high-quality evidence to support their decision-making to reduce the risk of ACLR failure for patients.

Previous systematic reviews and meta-analyses have sought to investigate the influence of single risk factors on ACLR failure, including participation in high-risk sports, return-to-sport protocols, patient sex, graft characteristics, and others.[2,19-22] Therefore, the purpose of this study was to (1) assess the consistency of risk factor reporting for ACLR failure after primary reconstruction, (2) identify risk factors more frequently associated with ACLR failure, and (3) help clinicians prevent reinjury in patients with risk factors for ACLR failure.

We hypothesized that there would be significant heterogeneity in reporting risk factors and that allograft use would significantly affect ACLR failure.

Methods

We utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to conduct a systematic review. PubMed/MEDLINE, EMBASE, and CENTRAL (Cochrane) databases were queried using an a priori search algorithm with the terms ("anterior cruciate ligament" OR "ACL") AND "reconstruction" AND ("revision" OR "rerupture" OR "failure" OR "reoperation") AND "risk" NOT "systematic review" NOT "meta-analysis" on November 3, 2020. Duplicates were removed, and titles were screened for a focus on ACLR. The remaining studies were assessed for eligibility. Inclusion criteria included (1) clinical studies of primary ACLR, (2) risk factors for failure or reoperation, (3) minimum follow-up of 1 year, and (4) manuscripts published within 6 years of our initial search. Exclusion criteria included (1) studies of revision ACLR, (2) studies that do not report risk factors for failure, (3) non-English studies, (4) case series <10 patients, (5) multiligament reconstruction, (6) <1-year follow-up, and (7) studies published before November 2020.

Studies defining ACLR failure as revision surgery and studies defining ACLR failure as graft failure were analyzed. A distinction between the 2 modes of failure was included in the analysis because there can be patients with grafts who do not heal well after surgery, tear partially, or have some elements of structural abnormality that may or may not clinically impact a patient but do not merit undergoing revision surgery. This included extraction of risk factors and evaluation of their statistical significance. The most frequently investigated risk factors were tabulated and summarized to assess agreement and significance across studies. Case-control studies were excluded from calculation or pooling of failure rates.

Results

Study Selection

The literature search yielded 1,304 studies, which included 456 duplicates (Fig 1). A title screen was performed on the remaining 848 studies, which excluded 561 studies that did not focus on ACLR. The remaining 287 studies were assessed for eligibility. After screening, 76 studies met criteria for full-text evaluation. From these, an additional 44 studies were excluded for having a mixed definition of ACLR failure, most often not separating their analyses for revision surgery and graft failure. Ultimately, a total of 22 studies defining ACLR failure as revision surgery and 10 studies defining ACLR failure as graft failure were analyzed in this study.

Failure Rates and Risk Factors

Failure rates across included studies ranged from 1.80% to 8.40% for failure defined as revision surgery and 3.50% to 34.60% for failure defined as graft failure. Risk factors were included in the analysis if they were investigated in 2 or more studies. Ten risk factors were included in the review for 22 studies defining ACLR failure as revision surgery, and 8 risk factors were included in the review for 10 studies defining ACLR failure as graft failure. Tables 1 and 2 include all studies and risk factors regardless of the statistical technique applied. Table 3 lists the level of evidence, type of study, and number of patients investigated for each included study. There were 6 Level II studies, 20 Level III studies, and 6 Level IV studies consisting of 14 cohort studies, 11 case-control studies, and 7 case series included in the analysis covering a total of 218,836 patients. The sample size and percent significant of each individual risk factor across all included studies are also illustrated in Figure 2.

Risk Factors for Revision Surgery

In studies defining ACLR failure as revision surgery, the most commonly studied risk factors were age and sex, which were investigated in 64% of studies. Younger age was found to be significant in 79% of studies. Studies varied in their age brackets but were generally between 18 and 25 years of age, with the younger age brackets experiencing statistically

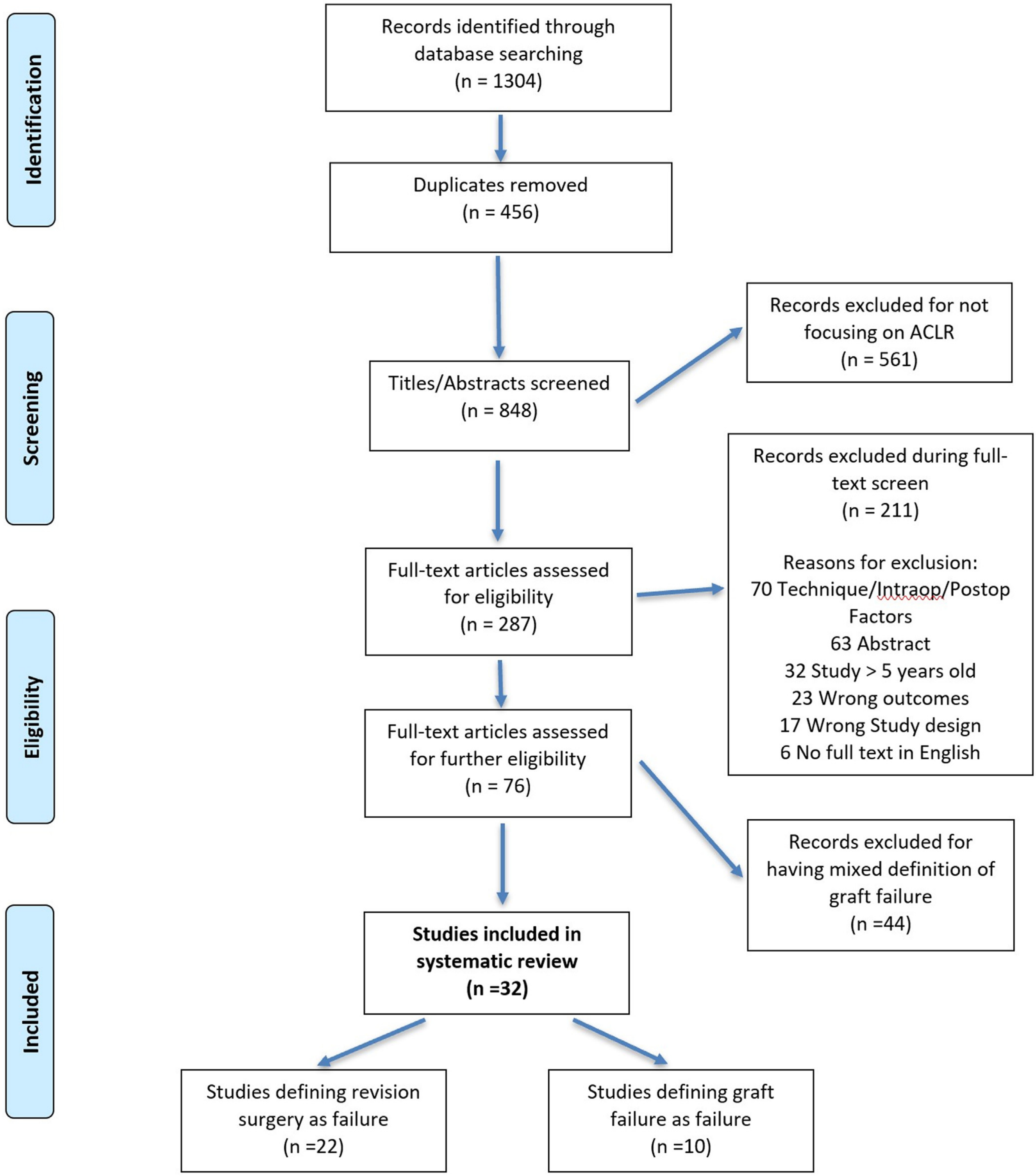

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart exhibiting inclusion and exclusion technique for extraction.

significant increased rates of revision surgery. Sex was significant in 36% of studies. Three studies found males at higher risk for revision surgery,[14,16,25] while two found females at higher risk.[15,27] The second most commonly studied risk factors were anthropometric measurements (e.g., BMI, height, and weight) and concomitant knee injuries, which were investigated in 41% of studies and significant in 22% of studies.

Table 1. Risk Factors Associated With Revision Anterior Cruciate Ligament Reconstruction

Study (First Author, Year)	Age	Sex	Anthropometric Measurements	Concomitant Knee Injury	Graft Characteristics**	Increased LPTS/MPTS	Activity Type	Race	Time to Surgery	Smoking	Factors Included
Yabroudi 2016[6]	✓	✗	✗ 1	✗	✓				✗		**6/10**
Henle 2018[7]	✓	✗	✗ 1				✓		✗	✗	**6/10**
Andernord 2015[23]	✓	✗	✗ 1,2,3				✓			✗	**5/10**
Pullen 2016[8]	✓	✗		✓				✗		✗	**5/10**
Maletis 2016[14]	✓	✓	✓ 1		✓			✓			**5/10**
McCarthy 2017[15]	✓	✓	✗ 1	✗	✗						**5/10**
Mitchell 2018[9]	✗	✗	✗ 1	✓		✓					**5/10**
Snaebjörnsson 2019[24]	✓	✗	✓ 1				✓			✗	**5/10**
Sutherland 2019[16]	✓	✓					✗	✗	✓		**5/10**
Tejwani 2015[25]	✓	✓	✗ 1		✓						**4/10**
Grassi 2019[17]	✗	✗		✗		✓					**4/10**
Pierce 2019[18]	✗	✗			✓		✗				**4/10**
Desai 2017[26]	✓	✗		✗							**3/10**

(continued)

Table 1. Continued

Study (First Author, Year)	Age	Sex	Anthropometric Measurements	Concomitant Knee Injury	Graft Characteristics**	Increased LPTS/MPTS	Activity Type	Race	Time to Surgery	Smoking	Factors Included
Riff 2017[27]	✓	✓			✓						**3/10**
Inderhaug 2020[28]			✗ **1**		✗						**2/10**
Snaebjörnsson 2019[29]				✗					✓		**2/10**
Carr 2018[30]				✗							**1/10**
Cooper 2019[31]						✗					**1/10**
Jaecker 2018[32]						✓					**1/10**
Navarro 2019[33]								✓			**1/10**
Lee 2018[34]						✓					**1/10**
Slagstad 2020[35]				✗							**1/10**
% Studies analyzed	14/22 64%	14/22 64%	9/22 41%	9/22 41%	7/22 32%	5/22 23%	5/22 23%	4/22 18%	4/22 18%	4/22 18%	
% Significant	11/14 79%	5/14 36%	2/9 22%	2/9 22%	5/7 71%	4/5 80%	3/5 60%	2/4 50%	2/4 50%	0/4 0%	

NOTE. Factors included by any statistical analysis. Studies are sorted by the number of included factors in the analysis. Graft characteristics include but are not limited to allograft versus autografts, diverse graft types (bone—patellar tendon—bone, hamstring, quadricep), preparation and preservation techniques, fixation technique, sizing, and the use of radiation. Green checkmark = significant risk factor, red X = nonsignificant risk factor, blank = factor not included. 1, body mass index; 2, height; 3, weight.

LPTS, lateral posterior tibial slope; MPTS, medial posterior tibial slope.

Table 2. Risk Factors Associated With Anterior Cruciate Ligament Reconstruction Graft Failure

Study (First Author, Year)	Graft Characteristics**	Concomitant Knee Injury	Younger Age	Sex	Higher Activity Level	Activity Type	BMI	Increased LPTS/MPTS	Factors Included
Kaeding 2015[10]	✓	✗	✓	✗	✓	✗			**6/8**
Astur 2019[11]	✗	✗	✗	✗	✓	✗			**6/8**
Tanaka 2018[12]	✗	✗	✗		✗		✗		**5/8**
Cruz 2017[36]	✗	✗	✗	✗			✗		**5/8**
Gans 2018[37]				✓		✓			**2/8**
Akada 2019[38]		✗							**1/8**
Patel 2019[39]							✗		**1/8**
Sauer 2019[13]								✓	**1/8**
								*	
Christensen 2015[40]								✓	**1/8**
Wolf 2015[41]	✗								**1/8**
% Studies analyzed	5/10 50%	5/10 50%	4/10 40%	4/10 40%	3/10 30%	3/10 30%	3/10 30%	2/10 20%	
% Significant	1/5 20%	0/5 0%	1/4 25%	1/4 25%	2/3 67%	1/3 33%	0/3 0%	2/2 100%	

NOTE. Factors included by any statistical analysis. Studies are sorted by the number of included factors in the analysis. Green checkmark = significant risk factor, red X = nonsignificant risk factor, blank = factor not included. Increased LPTS was significant in the transportal anterior cruciate ligament reconstruction failure group and not the transtibial anterior cruciate ligament reconstruction failure group. Graft characteristics include but are not limited to allograft versus autografts, diverse graft types (bone—patellar tendon—bone, hamstring, quadricep), preparation and preservation techniques, fixation technique, sizing, and the use of radiation.

BMI, body mass index; LPTS, lateral posterior tibial slope; MPTS, medial posterior tibial slope.

Maletis et al.[14] found BMI <30 increased the risk for revision surgery, and Snaebjörnsson et al.[24] found increased risk for revision surgery with an overweight BMI categorization (25-30). Increased posterior tibial slope (PTS) had the highest rate of significance (80%) but was only examined by Level III retrospective case-control trials. The third most significant factor was graft characteristics (e.g., allograft vs bone—patellar tendon—bone [BPTB] autograft, high-dose radiation, and BioCleanse preparation technique), which were collectively investigated in 32% of studies (7/22) and found significant in 71% (5/7). Graft characteristics found to be significant were allograft use in 83% (5/6 studies), high-dose radiation in 50% (1/2), and BioCleanse preparation technique in the lone study that examined it (see Tables 6-7, "Allograft Versus Autograft Subanalysis," and "Allograft Preservation and Preparation Technique Subanalysis"). In these studies, characteristics such as graft size and donor age were not significant predictors of revision surgery.

The least investigated risk factors were race, time to surgery, and smoking; each was investigated in 18% of studies. Smoking was significant in 0% of studies, while race and time to surgery were significant in 50% (2/4). With regard to race, Navarro et al.[33] studied a group of universally insured patients undergoing ACLR and found at >3.5 years postoperatively that those who were Asian, Hispanic, or Black underwent revision ACLR at lower rates than White counterparts (hazard ratio = 0.72, 0.83, 0.23, respectively). The 5-year ACLR

Table 3. Level of Evidence of All Included Studies Risk Factors Included by Any Statistical Analysis

Study (First Author, Year)	Level of Evidence	Study Type	Number of Patients
Yabroudi 2016[6]	Level III	Case Control	251
Henle 2018[7]	Level IV	Case Series	381
Andernord 2015[23]	Level II	Prospective Cohort	16,930
Pullen 2016[8]	Level III	Retrospective Cohort	16,336
Maletis 2016[14]	Level II	Prospective Cohort	21,304
McCarthy 2017[15]	Level III	Case Series	2,109
Mitchell 2018[9]	Level III	Case Control	487
Snaebjörnsson 2019[24]	Level II	Prospective Cohort	58,692
Sutherland 2019[16]	Level IV	Case Series	14,926
Tejwani 2015[25]	Level III	Retrospective Cohort	5,968
Grassi 2019[17]	Level III	Case Control	43
Pierce 2019[18]	Level III	Case Control	312
Desai 2017[26]	Level III	Retrospective Cohort	17,682
Riff 2017[27]	Level IV	Case Series	2,450
Inderhaug 2020[28]	Level II	Prospective Cohort	4,029
Snaebjörnsson 2019[29]	Level II	Prospective Cohort	18,425
Carr 2018[30]	Level III	Case Control	1,967
Cooper 2019[31]	Level III	Case Control	634
Jaecker 2018[32]	Level III	Case Control	57
Navarro 2019[33]	Level III	Retrospective Cohort	27,258
Lee 2018[34]	Level III	Case Control	64
Slagstad 2020[35]	Level III	Retrospective Cohort	1,364
Kaeding 2015[10]	Level II	Prospective Cohort	2,488
Astur 2019[11]	Level IV	Case Series	1,376
Tanaka 2018[12]	Level III	Retrospective Cohort	358
Cruz 2017[36]	Level IV	Case Series	103
Gans 2018[37]	Level III	Retrospective Cohort	1,105
Akada 2019[38]	Level III	Case Control	426
Patel 2019[39]	Level III	Retrospective Cohort	1,056
Sauer 2019[13]	Level III	Case Control	60
Christensen 2015[40]	Level III	Case Control	58
Wolf 2015[41]	Level IV	Case Series	137

BMI, body mass index; LPTS, lateral posterior tibial slope; MPTS, medial posterior tibial slope.

revision rate found by Maletis et al.[14] was similarly lower for Black (hazard ratio = 0.55) compared to White patients.

A time to surgery of less than 1 year in Sutherland et al.[16] and less than 6 months, 1 year, and 2 years in Snaebjörnsson et al.[29] was associated with an increased risk for revision surgery. Finally, activity type was investigated in 23% and significant in 60% of studies. Activities found to be significant risk factors for revision surgery in single studies included activities with a Tegner score >5 (Appendix Table 1, available at www.arthroscopyjournal.org), soccer, floorball, downhill skiing, handball, football, gymnastics, and participating in contact sports.[7,23,24]

Risk Factors for Graft Failure

In studies defining ACLR failure as graft failure, the most commonly studied risk factors were graft characteristics and concomitant knee injury, which were investigated in 50% of studies. Graft characteristics were significant in 1 of 5 studies, with allograft being a significant predictor of graft failure compared to BPTB autograft. Graft characteristics that were insignificant were fixation methods, graft diameter, graft thickness, notch dimensions, and single- versus double-bundle grafts. Concomitant knee injuries were significant in 0% of studies. The second most studied risk factors were age and sex, which were both investigated in 40% of studies and significant in 25%. Gans et al.[37] found females at higher risk for graft failure, and Kaeding et al.[10] found younger age as a risk factor for failure. The least investigated risk factor was LPTS/MPTS, which was investigated in 20% of studies. Increased LPTS/MPTS was found to have the highest rate of significance (100% of studies). However, it should be noted none of these studies were randomized control trials, and all studies were Level III retrospective case-control trials. High-risk PTS cutoff values for graft failure were not identified in these studies. Higher activity level, activity type, and BMI were investigated in 30% of studies. They were found to be significant in 67%, 33%, and 0% of studies, respectively. Male football players, female gymnasts, and female soccer players were associated with higher risk of graft failure.[37]

Fig 2. The colored visual scale depicts sample size and percentage of studies for which risk factors were found significant for studies defining anterior cruciate ligament reconstruction failure as revision surgery and graft failure. Circle size corresponds to increasing number of studies analyzing the specified risk factor, and shade from white to dark green corresponds to increasing percent significant.

Posterior Tibial Slope Subanalysis

The most consistent predictor of ACLR graft failure or revision surgery in this analysis was PTS. PTS was investigated in 7 of 32 (22%) studies and significant in 86% (6/7) (Tables 4-5). PTS is measured from lateral radiographs or sagittal magnetic resonance imaging

Table 4. Posterior Tibial Slope Subanalysis as a Risk Factor for Revision Anterior Cruciate Ligament Reconstruction

Study (First Author, Year)	LPTS Significant	MPTS Significant	Mean PTS Significant	Study Population	PTS Cutoff	Measurement Modality
Grassi 2019[17]	Primary (4.8 ± 3.0) vs revision (11.4 ± 4.2)	Primary (4.4 ± 2.7) vs revision 9.4 (6.6 to 13.1)	N/A	Primary (N = 43) Revision (N = 43)	LPTS ≥7.4 identified as having a sensitivity of 88% and specificity of 84%	MRI method by Grassi et al.[43]
Jaecker 2018[32]	Primary (4.6°) vs revision (7.3°)	Primary (4.1°) vs revision (6.7°)	N/A	Overall (N = 57)	LPTS ≥10 MPTS ≥8	MRI method by Hashemi et al.[44]
Lee 2018[34]	N/A	N/A	Mean PTS primary (10.9 ± 3.1) vs revision (13.2 ± 2.5)	Overall (N = 64)	Mean PTS ≥12	Radiographs
Mitchell 2018[9]	N/A	Primary (10.3 ± 3.2) vs revision ACLR (11.0 ± 3.4)	N/A	Primary (N = 363) Revision (N = 124)	N/A	Radiographs
Cooper 2019[31]	Differences between primary vs revision groups were found, but not statistically significant	No difference between primary vs revision groups	N/A	Primary (N = 317) Revision (N = 317)	LPTS ≥12 LPTS ≥13	MRI method by Hashemi et al.[44]

ACLR, anterior cruciate ligament reconstruction; LPTS, lateral posterior tibial slope; MPTS, medial posterior tibial slope; MRI, magnetic resonance imaging; PTS, posterior tibial slope.

Table 5. Posterior Tibial Slope Subanalysis as a Risk Factor for Graft Failure

Study (First Author, Year)	LPTS Significant	MPTS Significant	Mean PTS Significant	Study Population	PTS Cutoff	Measurement Modality
Sauer 2019[13]	Primary (7.1) vs graft failure (8.6)	N/A	N/A	Overall (N = 1480)	N/A	MRI method by Hudek et al.[45]
Christensen 2015[40]	Primary (6.5) vs graft failure (8.4)	N/A	N/A	Overall (N = 58)	N/A	MRI method by Hashemi et al.[44]

LPTS, lateral posterior tibial slope; MPTS, medial posterior tibial slope; MRI, magnetic resonance imaging; PTS, posterior tibial slope.

(MRI) cuts, with no standardized measurement technique. PTS can be measured by the angle between a line parallel to the medial or lateral tibial plateau and a line perpendicular to the anterior tibial cortex, posterior tibial cortex, or longitudinal tibial axis (Fig 3).[42] LPTS was significant in 4 studies,[13,17,32,40] MPTS was significant in 3 studies,[9,17,32] and mean PTS was significant in 1 study.[34] MRI-based LPTS studies found cutoff values of 7.4°[17] and 10° to be significant[32] and found higher cutoff values of 12° and 13° to be nonsignificant.[31] MRI-based MPTS had a significant cutoff of 8° in 1 study,[32] and radiographic-based mean PTS had a significant cutoff of 12° in another study.[34] Finally, in only 1 study was LPTS and MPTS found to be an insignificant predictor of ACL revision surgery.[31]

Allograft Versus Autograft Subanalysis

Eight of 32 studies examined graft type (i.e., allograft, autograft, or hybrid) as a risk factor for either revision ACLR (6 studies) or graft failure (2 studies), as seen in Tables 6 and 7. Six studies found graft type significant (75%) (6/8). Six studies specifically examined allografts versus autografts. Of these, 5 studies (80%) found allografts to be a significant risk factor for retear or revision ACLR,[6,10,14,18,27] with 4 of these studies comparing allografts to BPTB autografts.[10,14,18,27] Another study found graft type (allograft vs autograft vs hybrid) not significant.[36] Finally, allograft type was examined as a risk factor for revision surgery in 2 studies,[15,25] and BPTB allografts compared to soft tissue allografts were found significant in 1 study.[25] The other study found no difference between Achilles, tibialis anterior, tibialis posterior, and hamstring allografts.[15]

Allograft Preservation and Preparation Technique Subanalysis

Two studies controlled for allograft graft treatment and preservation techniques (Table 8).[25,27] One study found radiation doses >1.8 Mrad to be a significant predictor of revision surgery. The other found low-dose irradiation (1.2 Mrad) was insignificant compared to nonirradiated allografts. Furthermore, the graft cleansing technique was examined in 1 study. BioCleanse was the only cleansing technique found significant.[25] AlloWash and AlloTrue were not found significant.

Risk Factor Inclusivity and Quality of Papers

Each study was assessed for quality by Methodological Index for Non-Randomized Studies criteria (Appendix Table 2, available at www.arthroscopyjournal.org) by 2 orthopaedic surgery residents (K.C. and N.D.). In studies defining ACLR failure as revision surgery, no study controlled for all 10 risk factors. The most inclusive studies were published by Yabroudi et al.[6] and Henle et al.,[7] which both investigated 6 risk factors. Seven studies investigated 5 factors.[8,9,14-16,23,24] Three studies investigated 4 factors[17,18,25] Two studies investigated 3 factors.[26,27] Two studies investigated 2 factors.[28,29] Six studies investigated 1 factor.[30-35] In studies defining ACLR failure as graft failure, no study controlled for all 8 risk factors. The most inclusive studies were those published by Kaeding et al.[10] and Astur et al.,[11] which both investigated 6 risk factors. Two studies investigated 5 factors.[12,36] The study published by Gans et al.[37]

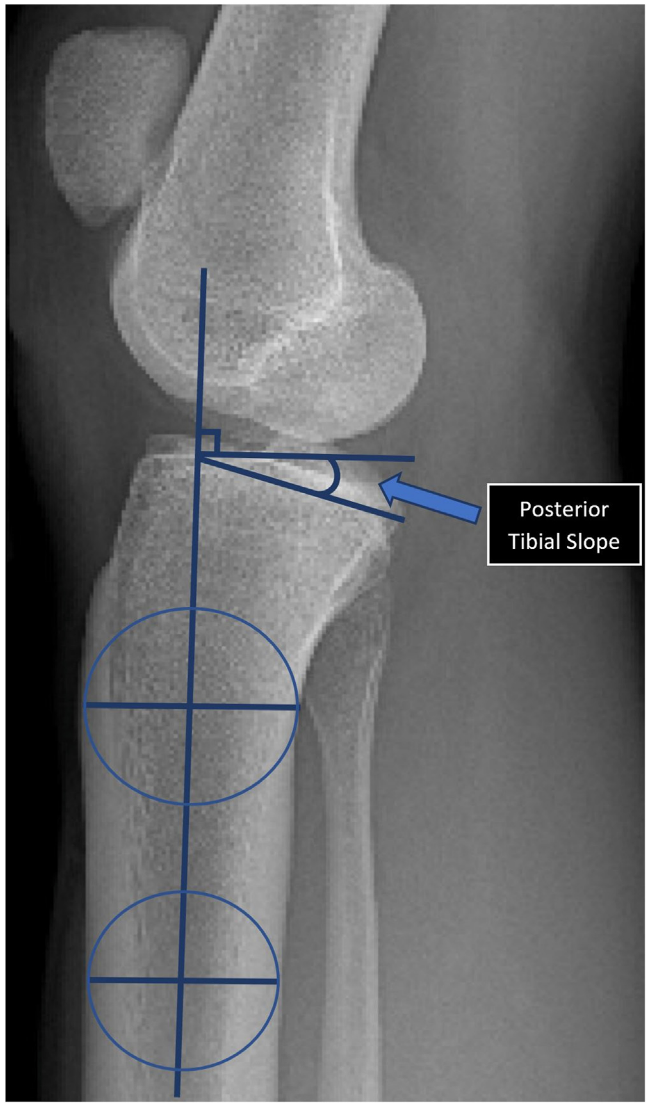

Fig 3. This image shows medial posterior tibial slope being calculated using a lateral radiograph of a right knee by measuring the angle between a line parallel to the tibial plateau and a line perpendicular to the longitudinal tibial axis. The longitudinal tibial axis is defined as 2 points at a distance halfway between the anterior and posterior cortex, one of which is at the lower border of the tibial tuberosity and one 10 cm below.

Table 6. Subanalysis of Allograft Versus Autograft as a Risk Factor for Revision Anterior Cruciate Ligament Reconstruction

Study (First Author, Year)	Significant Factors	Study Population	Allograft Types	Patient Age
Pierce 2021[18]	Tibialis anterior and hamstring allografts compared to BPTB autograft	Overall (N = 312) 8.0% allograft (N = 25)	76% tibialis anterior allograft 24% hamstring allograft	24 years (range, 9-62)
Maletis 2016[14]	Allografts (age <40) compared to BPTB autografts Hamstring autografts compared to BPTB autografts	40.7% allograft (N = 8,671) 32.0% hamstring autograft (N = 6,823) 24.7% BPTB autograft (N = 5,260)	N/A	27.0 years (IQR, 18.6-37.6)
Yabroudi 2017[6]	Allograft compared to autograft	Overall (N = 251) 43.8% allograft (N = 110)	N/A	26.1 ± 9.9 years
Tejwani 2015[25]	BPTB allograft compared to soft tissue allografts	100% allograft (N = 5,968)	62.9% soft tissue 19.9% Achilles tendon 17.2% BPTB	34.1 years (IQR, 24.1-22.9)
Riff 2017[27]	BPTB allograft compared to BPTB autograft	28.1% allograft (N = 690) 61.6% BPTB autograft (N = 1,510) 1.0% hamstring autograft (N = 25)	97.7% BPTB allograft (N = 674) 2.3% hamstring allograft (N = 16)	29.3 ± 15.1 years
McCarthy 2017[15]	Soft tissue allograft types	Overall (N = 1,760) 23.2% allograft (N = 409)	80.9% allograft Achilles 7.8% allograft tibialis anterior 7.3% allograft hamstring 4.0% allograft tibialis posterior	29.6 ± 12.0 years

BPTB, bone−patellar tendon−bone; IQR, interquartile range.

investigated 2 factors. Five studies investigated 1 factor.[13,38-41]

Discussion

This systematic review found the factors that are well studied and commonly predictive of ACLR revision surgery include younger age, graft characteristics (allograft vs BPTB autograft, high-dose radiation, and BioCleanse preparation technique), PTS, and activity type (soccer, football, gymnastics, contact sports, floorball, downhill skiing, handball, and activities with Tegner score >5). The risk factors that are well studied and commonly predictive of ACLR graft failure include higher activity level and PTS. Lastly, risk factors that are well studied but not commonly predictive of ACLR failure include sex (both revision surgery and graft failure cohorts), concomitant knee injury (both), anthropomorphic measurements (both), smoking (revision), graft characteristics (graft failure), age (graft failure), and activity type (graft failure). There was a high level of heterogeneity in reported risk factors between studies, with 19 of 32 (59.4%) studies controlling for less than half of the investigated variables. Given this heterogeneity in the current orthopaedic literature, we believe future studies would benefit from a more comprehensive and cohesive approach to examining risk factors for ACLR failure given the present study findings. This is highly evident, especially in the studies examining PTS and graft selection, where PTS was measured with different methodologies and imaging modalities, and graft comparisons were variable between each examined study, with a paucity of data examining allograft preparation techniques.

Table 7. Subanalysis of Allograft Versus Autograft as a Risk Factor for Graft Failure

Study (First Author, Year)	Significant Factors	Study Population	Patient Age
Kaeding 2015[10]	Allograft vs BPTB autograft	Overall (N = 2,683) 17.3% allograft (N = 466)	27.4 ± 11.4 years
Cruz 2017[36]	Graft type	18.4% allograft (N = 19) 78.6% autograft (N = 81) 2.9% hybrid (N = 3)	12.1 ± 1.8 years

BPTB, bone−patellar tendon−bone.

Table 8. Subanalysis of Preservation and Preparation Techniques as a Risk Factor for Revision Anterior Cruciate Ligament Reconstruction

Study (First Author, Year)	Significant Factors	Study Population	Patient Age	Graft Treatment
Tejwani 2015[25]	Graft irradiation >1.8 Mrad vs Mrad <1.8 BioCleanse graft processing	Overall (N = 5,968)	34.1 years (IQR, 24.1-22.9)	**Radiation Dose** 19.2% irradiation dose >1.8 Mrad (N = 1,146) 61% irradiation dose <1.8 Mrard (N = 3,637) 19.8% no irradiation (N = 1,185) **Cleansing Technique** 6.1% BioCleanse (N = 367) 38.2% AlloWash or AlloTrue (N = 2,278)
Riff 2017[27]	Low-dose irradiation (1.2 Mrad)	Overall (N = 2,450)	29.3 ± 15.1 years	**Radiation Dose** 82.3% low-dose irradiated (1.2 Mrad) (N = 555) 17.7% nonirradiated (N = 119)

The most consistent predictor of ACLR graft failure or revision surgery was PTS, which was investigated in 7 of 32 of all studies (22%) and significant in 86% (6/7). LPTS was significant in 4 studies, MPTS was significant in 3 studies, and mean PTS was significant in 1 study. Dejour and Bonnin[46] found for every 10° increase in PTS, there was a resultant 6-mm increase in anterior tibial translation. Similarly, there is a significant increase in the odds ratio for graft failure with incremental increases in LPTS.[40] Increased anterior tibial translation leads to an increase in ACL strain, which predisposes to failure and revision, as shown here. In this review, studies found significant MRI-based LPTS cutoff values of 7.4°, 8°, and 10° and nonsignificant cutoffs of 12° and 13°. MRI-based MPTS had a significant cutoff of 8° in 1 study.[32] In only 1 MRI study were LPTS (with cutoffs of 12° and 13°) and MPTS found to be an insignificant predictor of ACL revision surgery, but the authors still found an increased proportion of patients with lateral PTS ≥12° in the revision group.[31] The authors of this review suspect that the thresholds in that study were too high to find a significant difference, as the other studies examining PTS using the same MRI methodology found a significant difference,[32,40] including 1 study showing LPTS >10° and MPTS >8° increased the risk of revision (see Tables 4-5).[32] One of the radiograph-based studies found a significant cutoff of 12° for mean PTS,[34] which was the highest significant cutoff in this review. Lee et al.[47] published a study showing significant increases in PTS measurements using lateral radiographs versus sagittal plane MRI in the same patient population, which was reflected by higher mean cutoffs in the radiograph group compared to MRI in our review. Therefore, the true cutoff for PTS is likely different if measured by MRI versus radiography and is likely higher if measured radiographically. While increased PTS has clearly shown importance as a risk factor for ACLR failure in the orthopaedic literature, the degree of PTS that puts a patient at risk for ACLR failure remains to be exactly specified. Therefore, the authors believe the current literature would be augmented by future studies examining PTS with a more consistent, clearly defined, and easily clinically applicable methodology for each imaging modality. This research may help show which patients could benefit from staged or concomitant procedures such as a high tibial osteotomy for correction of PTS.

Graft options in ACLR are vast and continue to expand, including allograft versus autografts, diverse graft types, preparation and preservation techniques, fixation technique, sizing, and the use of radiation. Seven out of 22 studies (32%) defining ACLR failure as revision surgery analyzed graft characteristics, and 71% (5/7) found graft characteristics, particularly graft selection, significant. Graft selection characteristics found to be significant were allograft use in 83% (5/6 studies), high-dose radiation >1.8 Mrad in 50% (1/2), and BioCleanse preparation technique in the lone study that examined it (see Tables 6-7, "Allograft Versus Autograft Subanalysis," and "Allograft Preservation and Preparation Technique Subanalysis"). In the 10 studies defining ACLR failure as graft failure, graft characteristics were investigated in 50%. In the 2 studies examining graft type (e.g., allograft vs autograft), 1 study found allograft to be a significant predictor of graft failure compared to BPTB autograft (Table 7). For the 5 studies finding graft characteristics as a significant predictor for revision and 1 study finding them a significant predictor of graft failure, the most cited predictor was allograft usage as opposed to autograft, which was significant in 5 studies and trending toward significance ($P = .076$) in another (Tables 6-7).[6,10,14,18,25,27] In support of this finding, in vivo sheep studies have shown allografts have delayed revascularization and recellularization, lower structural and mechanical properties, and increased anteroposterior laxity compared to autografts.[48] For patients with other factors that increase their risk of ACLR failure, the authors recommend that their surgeon consider using autograft if possible.

Additional graft factors found to be significant in ACLR failure in 1 study were radiation >1.8 Mrad and use of BioCleanse processing versus AlloWash or AlloTrue.[25] Another study found low-dose irradiation (1.2 Mrad) insignificant as a predictor of revision surgery.[27] Application of allograft radiation has been reviewed extensively, with estimates in the literature of <2.2 Mrad not significantly increasing failure rates, while levels higher than 2.5 were associated with increased laxity, decreased load to failure, and elevated clinical failure rates.[49,50] Our results support these findings and agree that low-dose radiation is safe for allograft preparation but likely lower than previous literature-suggested values. Other graft characteristics that were insignificant predictors of either graft failure or revision surgery that need further investigation due to limited examination by a small number of studies include graft diameter/thickness,[11,25,28] single versus double bundle,[12,41] graft donor age,[15,25] low-dose irradiation equivalent to 1.2 Mrad,[27] AlloWash/AlloTrue processing technique,[25] fixation method,[11] and notch dimensions.[41]

Overall, the authors believe the current literature would benefit from a more comprehensive study examining the plethora of available allograft characteristics and processing techniques available, as many studies do not report on these techniques. These factors, particularly allograft chemical and radiation processing techniques, may potentially serve as a contributor to allografts faring worse than autografts throughout the literature. If these risk factors in processing were clearly delineated and potentially eliminated, improvements in allograft outcomes could allow surgeons to use them and decrease operative time, graft site morbidity, and recovery time.

Younger age was the most studied variable and was included in 14 of 22 ACLR studies defining failure as revision surgery (64%) and was found to be significant in 79% (11/14). Four of 10 (40%) studies defining ACLR failure as graft failure studied age, while 25% (1/4) found it to be significant. The pediatric population has been consistently reported to have higher rates of ACLR revision.[51] For patients who have not yet reached skeletal maturity, many alternate reconstruction techniques exist, including physeal sparing, partial transphyseal, and complete transphyseal.[51,52] The higher rate of ACLR revision is likely due to a multitude of factors, including higher participation in athletics, difficulty in adhering to postoperative protocols, and alternate graft fixation techniques.[53,54] While some of these factors are outside of the control of the surgeon, the authors believe autograft selection in pediatric athletic populations may serve as a measure to mitigate the risk of ACLR failure for these patients.

Activity type was investigated in 5 of 22 (23%) graft revision studies and significant in 60% (3/5). In the graft failure studies, activity type was included in 3 of 10 (30%) and significant in only 33% (1/3). Activity types found to be significant in single studies include patients with a Tegner score >5 (as shown in Appendix Table 1, available at www.arthroscopyjournal.org; heavy labor, cycling, cross-county skiing, jogging on uneven ground ≥2 times per week), soccer players, football players, gymnasts, and those participating in contact sports.[7,23,24,37] Finally, activity level was studied in 3 of 10 (30%) studies defining ACLR failure as graft failure and reached significance in 67% (2/3). It stands to reason that increased activity frequency and intensity put elevated stress on ACLR grafts, leading to higher rates of revision surgery. Surgeons should use caution when clearing higher-demand athletes to return to their sport and counsel patients accordingly.

Sex, concomitant knee injury, and anthropomorphic measurements were found to not be predictors of ACLR failure in both groups, while smoking was not significant but only investigated in the revision surgery group. Sex was only significant in 33% of studies (6/18) and analyzed in 18 of 32 (56%). It is reported that females are at risk for higher rates of ACL tears, implicating a higher prevalence of deficits in dynamic neuromuscular knee control, among other factors, although this does not appear to affect the risk of ACLR failure on a large scale, potentially due to the effectiveness of postoperative rehabilitation protocols.[22,27,55] Concomitant knee injury was significant in 14% (2/14) and analyzed in 14 of 32 (44%). Anthropomorphic measurements—including height, weight, and/or

BMI—were studied in 12 of 32 (38%) and significant in 17% (2/12). Finally, smoking was investigated in 4 of 22 (18%) studies defining ACLR failure as revision surgery and significant in 0% (0/4) despite smoking being a commonly cited predictor of poor healing.

Limitations

This systematic review comprises data extracted from prior published studies each with their own inherent limitations. Our inclusion/exclusion criteria sought the most updated and relevant studies, but the review was only able to identify Level II, Level III, and Level IV studies from which to draw conclusions. Further, it is plausible that useful studies and other important risk factors were omitted. Only the most commonly reported factors were included in our analysis; therefore, potentially important but lesser studied variables may have been excluded. Additionally, a high level of heterogeneity between studies was observed regarding risk factor reporting. Nineteen of 32 (59.4%) studies controlled for less than 50% of the investigated variables, including 11 of 19 (57.9%) of these, which only controlled for 1 variable. Furthermore, it is possible that different surgical techniques may have different risk factors for failure, and this review was not able to fully evaluate this nuance. Finally, the variance of demographics and follow-up durations in each study influences the risk factor analysis. Socioeconomic barriers to surgery could have affected the results of each study.

Conclusions

Age, PTS, use of allograft, and activity level are significant preoperative risk factors that should be considered when attempting to prevent reinjury in ACLR candidates. Studies investigating risk factors for ACLR failure often fail to control for confounding variables that can influence outcomes.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: N.A.T. reports personal fees from DJ Orthopaedics outside the submitted work. J.C. is a board member of the AOSSM, AANA, and International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine; is a paid consultant for Arthrex; and receives personal fees from CONMED Linvatec, Ossur, and Smith & Nephew outside the submitted work. A.B.Y. receives personal fees from AlloSource, JRF Ortho, CONMED Linvatec, and Olympus; has received grants from Arthrex and Vericel; has stocks with Patient IQ; and receives nonfinancial support from Organogenesis, Patient IQ, Smith & Nephew, and Sparta Biomedical outside the submitted work. All other authors (J.L., J.R.M., K.C., N.D., Z.W., R.Y.D.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix Table 1. Tegner Activity Score

Please indicate the **HIGHEST** level of activity you are able to participate in **CURRENTLY**.

Level 10	Competitive sports—soccer, football, rugby (national elite)
Level 9	Competitive sports—soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball
Level 8	Competitive sports—racquetball, squash or badminton, track and field athletics (jumping, etc.), downhill skiing
Level 7	Competitive sports—tennis, running, motorcars speedway, handball
	Recreational sports—soccer, football, rugby, ice hockey, basketball, squash, racquetball, running
Level 6	Recreational sports—tennis and badminton, handball, racquetball, downhill skiing, jogging at least 5 times per week
Level 5	Work—heavy labor (construction, etc.)
	Competitive sports—cycling, cross-country skiing
	Recreational sports—jogging on uneven ground at least twice weekly
Level 4	Work—moderately heavy labor (e.g., truck driving, etc.)
	Recreational sports—cycling, cross-country skiing, jogging on even ground at least twice weekly
Level 3	Work—light labor (nursing, etc.)
	Competitive and recreational sports—swimming, walking in forest possible
Level 2	Walking on uneven ground possible, but impossible to backpack or hike
Level 1	Work—sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of knee problems

Appendix Table 2. Methodological Index for Non-Randomized Studies Criteria of All Included Studies

Risk factors included by any statistical analysis.

	A clearly stated Aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Yabroudi 2016[6]	2	2	2	2	2	2	2	2	2	2	2	2	24
Henle 2018[7]	2	2	2	2	2	2	2	2	2	2	1	2	23
Andernord 2015[23]	2	2	2	2	2	2	2	2	2	2	1	2	23
Pullen 2016[8]	2	2	2	1	2	2	2	2	2	2	1	2	22
Maletis 2016[14]	2	2	2	2	2	2	2	2	2	2	1	2	23
McCarthy 2017[15]	2	2	2	2	2	2	2	2	2	2	1	2	23
Mitchell 2018[9]	2	2	2	2	2	2	2	1	2	2	1	2	22
Snaebjörnsson 2019[24]	2	2	2	2	2	2	2	2	2	2	2	2	24
Sutherland 2019[16]	2	2	2	2	2	2	2	2	2	2	2	2	24
Tejwani 2015[25]	2	2	2	2	2	2	2	2	2	2	1	2	23
Grassi 2019[17]	2	2	2	2	2	2	2	2	2	2	2	2	24
Pierce 2019[18]	2	2	2	1	2	2	2	1	2	2	1	2	21
Desai 2017[26]	2	2	2	2	2	2	2	2	2	2	2	2	24
Riff 2017[27]	2	2	2	1	2	2	2	1	2	2	1	2	21
Inderhaug 2020[28]	2	2	2	1	2	2	2	2	2	2	1	2	22
Snaebjörnsson 2019[29]	2	2	2	1	2	2	2	2	2	2	2	2	23
Carr 2018[30]	2	2	2	2	2	2	2	1	2	2	2	2	23
Cooper 2019[31]	2	2	2	2	2	2	2	1	2	2	2	2	23
Jaecker 2018[32]	2	2	2	2	2	2	2	2	2	2	2	2	24
Navarro 2019[33]	2	2	2	2	2	2	2	2	2	2	2	2	24
Lee 2018[34]	2	2	1	2	2	2	2	1	2	2	2	2	22

(continued)

Appendix Table 2. Continued

Risk factors included by any statistical analysis.

	A clearly stated Aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Slagstad 2020[35]	2	2	2	2	2	2	2	1	2	2	1	2	22
Kaeding 2015[10]	2	2	2	2	2	2	2	2	2	2	1	2	23
Astur 2019[11]	2	2	2	2	2	2	2	2	2	2	1	2	23
Tanaka 2018[12]	2	2	2	2	2	2	2	2	2	2	2	2	24
Cruz 2017[36]	2	2	2	1	2	2	2	1	2	2	1	2	21
Gans 2018[37]	1	2	2	1	2	2	2	2	2	2	1	2	21
Akada 2019[38]	2	2	2	2	2	2	2	2	2	2	1	2	23
Patel 2019[39]	2	2	2	2	2	2	2	2	2	2	1	2	23
Sauer 2019[13]	2	2	2	1	2	2	2	1	2	2	2	2	22
Christensen 2015[40]	2	2	2	2	2	2	2	2	2	2	2	2	24
Wolf 2015[41]	2	2	2	2	2	2	2	1	2	2	1	2	22