Avascular necrosis and time to surgery for unstable slipped capital femoral epiphysis: a meta-analysis

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Abstract

Background

Avascular necrosis (AVN) is a well-known complication of unstable slipped capital femoral epiphysis (SCFE) and its cause is multifactorial. Higher AVN rates have been reported with surgery undertaken between 24 hours to 7 days from the onset of symptoms. The current evidence regarding time to surgery and AVN rate remains unclear. The aim of our study was to investigate the rate of AVN and time to surgery in unstable SCFE.

Methods

A literature search of several databases was conducted. Eligibility criteria included all studies that reported AVN rates and time to surgery in unstable SCFE patients. We performed a meta-analysis using a random-effects model to pool the rate of AVN in unstable SCFE using different time to surgery subgroups (≤24 hours, 24 hours - 7 days and >7 days). Descriptive, quantitative and qualitative data were extracted.

Results

Twelve studies matched our eligibility criteria. In total, there were 434 unstable SCFE of which 244 underwent closed reduction (CR). The pooled AVN rates were 24% [95% CI: 16% - 35%] and 29% [95% CI: 16% - 45%] for the total and CR groups respectively. The highest AVN rates were with surgery between 24 hours to 7 days, 42% and 54% for the total and CR groups respectively. The lowest rates of AVN were with time to surgery within 24 hours (22% and 21% respectively) and >7 days (18% and 29% respectively). These differences were not statistically significant. There was significant within subgroup heterogeneity which was highest in the 24 hours - 7 days subgroup and lowest in the >7 days group.

Conclusions

The cumulative evidence does not support an association between AVN rate and time to surgery. The overall AVN rates were lower in unstable SCFE patients who had surgery within 24 hours and >7 days. However, treatment techniques were very variable and there was significant heterogeneity in the included studies. Multi-centre prospective controlled studies are required with well-defined time to surgery outcomes.

Level of Evidence: III/IV

Introduction

The incidence of slipped capital femoral epiphysis (SCFE) ranges between 0.33 – 24.58 per 100,000 globally and in the UK the incidence is 4.8 per 100,000 [1,2]. Unstable SCFE is an uncommon condition representing 9-14% of all SCFE [3,4]. Avascular necrosis (AVN) is the most significant complication in patients with unstable SCFE and the reported incidence is very variable in the literature. Timing from the onset of symptoms to surgery might play a major role in the development of AVN [3,5]. Other important surgical factors cited in the literature are closed reduction versus in-situ pinning [6,7], intracapsular hematoma decompression with percutaneous fixation techniques [8] and other recent reduction techniques such as surgical hip dislocation using the modified Dunn procedure [9].

According to the current literature, urgent reduction and fixation of unstable SCFE within the first 24 hours should always be attempted [5,10]. The aim of urgent unstable SCFE reduction is to reduce the displaced capital epiphysis that could potentially relieve the retinacular blood vessels kinking and restore the capital blood flow [10,11]. However, there is conflicting evidence in the literature supporting the value of urgent reduction of unstable SCFE. The reported AVN rates with closed gentle reduction and fixation of unstable SCFE within 24 hours vary widely between 0% to 80% [5,12].

The concept of an "unsafe window" in the treatment of unstable SCFE was first described by Kalogrianitis et al. [3]. It was defined as the timeframe between 24 hours to 7 days following the onset of symptoms. Significantly higher AVN rates were reported by Kalogrianitis et al. and Kohno et al. when surgery was undertaken during this timeframe compared to within the first 24 hours or after 7 days [3,7]. This was explained by the development of an inflammatory effusion within the hip joint that might jeopardise the tenuous blood supply to the femoral epiphysis [3] or increase the intra-capsular pressure due to the retained intra-capsular hematoma [7]. According to Kohno et al. [7], an unstable SCFE resembles in pathology and behaviour the intra-capsular femoral neck fracture. It was shown that the intra-capsular hematoma pressure following femoral neck fracture would increase to its highest pressure between 7 - 24 hours after trauma and this pressure would be constant at the same level at 48 hours followed by a trend to decline between 3-7 days [13].

The aim of our study was to systematically review the literature and report the AVN rate and time to surgery in unstable SCFE. The primary outcome analysis involved the rate of AVN.

Patients and methods

Data sources and search strategy

A search strategy was developed and literature search was performed. The databases searched included Medline, Ovid and Embase online libraries. The used search syntax was "(slipped capital femoral epiphysis) OR (SCFE)) AND (unstable) AND ((Avascular necrosis) OR (AVN)". Articles were not limited to any particular study design. Two authors independently assessed the eligibility of the identified studies. Any study that could be relevant based on the respective abstract was reviewed in full text. The language of the publications was restricted to English. We did not seek unpublished investigations.

Eligibility criteria

We considered any study design that documented time to surgery of unstable SCFE and reported the rate of AVN. An unstable SCFE was defined as a patient with severe pain that walking was not possible even with crutches, regardless of the duration of symptoms according to Loder et al. [12] classification. The diagnosis of AVN was defined by clinical and radiological findings.

Data extraction

Data were extracted into an excel table by two authors independently. Included studies reported AVN rates and to time to surgery within variable timeframes. The extracted data of interest were collected using the following timeframes: (1) surgery ≤24 hours, (2) >24 hours to 7 days and (3) after 7 days. The eligible studies included different treatment techniques for unstable SCFE such as PIS: pinning in-situ without reduction, CR: pinning with intentional (gentle)/unintentional (positional) closed reduction, OR: open reduction such as the Parsch technique [14] and SD: modified Dunn procedure with surgical hip dislocation [9].

The collected data included the total number of unstable SCFE, total AVN rate, total AVN rate according to time to surgery, length of follow-up in months and other statistically significant factors affecting the rate of AVN identified by the study such as severity of the slip, age, race, etc. The number of patients in the different treatment arms in each study were recorded and the total AVN rate for each treatment technique as well as the AVN rate according to time to surgery were recorded when available.

Two authors independently assessed the methodological quality of cohort studies according to key validity components that address selection, comparability, and exposure using the Newcastle-Ottawa scale to assess the quality of non-randomized studies. Any disagreement was resolved by consensus.

Statistical analysis

The rate of AVN in patients with unstable SCFE was computed for each study and converted into log odds (logit) of AVN to calculate the 95% confidence interval (CI) of the rate on the logit scale. The logit and its confidence interval was transformed back to rate estimates and Forest plots were constructed with 95% confidence interval for all studies to show the variation in the rate of AVN in patients with unstable SCFE across the included studies. A random effects model of the log odds (logit) of AVN in each study was used. The AVN rates were pooled using the inverse variance method. τ^2 was estimated using the restricted maximum-likelihood (REML) with the assumption of a common τ^2 in different subgroups. τ & τ^2 confidence intervals were estimated using Q-profile method. Hartung-Knapp adjustment was used for random effects model. Heterogeneity was measured using Q-test and Higgins and Thompson I^2 statistic. Continuity correction of 0.5 in studies with zero cell frequencies. Egger tests with funnel plot were performed to investigate publication bias. All statistical analyses were done using RStudio (2021.09.0+351 "Ghost Orchid" Release).

Analyses were performed to examine the effect of the different time intervals to surgery with the following subgroups: ≤24 hours, 24 hours to 7 days and >7 days. Additional sensitivity analyses (CR AVN analysis) were performed for unstable SCFE which had gentle or positional closed reduction (CR) and pinning as a total AVN rate and then grouped within the same previous timeframe subgroups.

Results

Yield of search strategy and eligible studies

The search strategy yielded 173 publications, after using built-in deduplication software this was reduced to 100 publications. Limiting the search to the English language yielded 91 publications. These 91 papers were used in the screening process. The screening process was done using title and abstract and 72 publications were removed. We considered 19 articles for full-text review to assess their final eligibility. During the full-text review, three further articles were identified from the reference lists. Of these 22 articles, 12 studies met our eligibility criteria and were included in the study. All papers excluded at this stage were excluded because they had no data on the time to surgery and resultant AVN rate. Figure 1 summarizes the process of identifying eligible studies. Five were retrospective cohort studies and seven studies were case series. There were no prospective cohort studies. The kappa statistics for inter-observer agreement on study eligibility was 1.0.

Characteristics of the included studies

Table 1 summarizes the characteristics and the rate of AVN in patients with unstable SCFE of the 12 studies included in our analyses. The studies included a total of 434 unstable SCFE. Of these 434 unstable SCFE, 101 were diagnosed with AVN. The individual sample sizes of the studies ranged from 14 to 91 unstable SCFE. The definition of AVN was similar in all 12 studies, utilizing radiographs for evidence of sclerosis and /or collapse. The follow-up period of the studies varied, but all studies except one had a follow-up period ≥ 12 months from the date of treatment to the appearance of AVN.

Quality assessment of the included studies

Table 2 summarizes the results of the different domains of study quality adapted from the Newcastle-Ottawa scale. All five studies scored the maximum numbers of stars on the selection and outcome domains. Two studies scored a total of nine out of a maximum of nine stars, whereas, the other three studies scored a total of eight. The kappa statistics for inter-observer agreement on these quality domains was 1.0.

Qualitative results of the meta-analysis

Figure 2 displays the pooled rate estimate of AVN in patients with unstable SCFE. A random-effects model meta-analysis of the 12 studies resulted in an overall pooled rate estimate of 24% [95% confidence interval (CI): 16% - 35%]. There was a substantial amount of between study heterogeneity (I^2=65%, p<0.01) and most of the heterogeneity was due to variability between studies rather than chance variability. The rate of AVN in patients with unstable SCFE across

the 12 studies ranged from 0 to 47%.

The studies included different techniques of treatment such as closed reduction (CR) either intentional or unintentional in 303 unstable SCFE, pinning in-situ (n=87 hips) and open reduction with or without subcapital osteotomy (n=36) and surgical hip dislocation using the modified Dunn procedure (n=8 hips).

The highest pooled AVN rate was in patients who had surgery after 24 hours and within 7 days of 42% [95% CI: 13 % - 78%] followed by the patients with time to surgery ≤24 hours of 21% [95% CI: 12% - 36%]. The lowest pooled AVN rate was with time to surgery > 7 days of 18% [95% CI: 6% - 42%]. These differences were not statistically significant. However, there was statistical significance within group heterogeneity. The highest heterogeneity was found in the timing subgroup >24 hours to 7 days (I^2= 63%, p = 0.02) followed by moderate heterogeneity in the subgroup ≤24 hours (I^2= 46%, p = 0.04). No significant heterogeneity was be found in the timing subgroup >7 days (I^2= 0%, p = 0.58%) (Figure 3).

Of the 12 studies, seven included 244 unstable SCFE that underwent closed reduction either intentional/gentle or unintentional/ positional with recorded details about time to surgery and AVN rates (CR AVN analysis). Sixty-three hips developed AVN with a pooled AVN rate of 29% [95% CI: 16% - 45%] (Figure 4). This closed reduction group was then analysed according to the same timing subgroups and 166 hips could be pooled for comparison of the AVN rates following the same timeframe subgroups ≤24 hours, between 24 hours to 7 days and > 7 days. The highest pooled AVN rate was between 24 hours to 7 days of 54% [95% CI: 4% - 97%] while the pooled AVN rate for closed reductions ≤24 hours and > 7 days were 21% [95% CI: 11% - 36%] and 29% [95% CI: 7% - 67%] respectively. The differences were not statistically significant (Figure 5). Similarly, there were significant heterogeneity within subgroups and the highest was between 24 hours - 7 days (I^2= 73%, p = 0.01%) followed by moderate heterogeneity in the timing subgroup ≤24 hours (I^2= 41%, p = 0.11%). No heterogeneity was found in the timing subgroup >7 days (I^2= 0%, p = 0.57%).

There was no evidence of publication bias from the funnel plots and the Egger tests.

Discussion

The magnitude of retinacular vessel kinking and disruption with the initial slip displacement is a main determinant of the residual blood supply to the femoral head [10,12]. Surgical factors that can be changed to decrease the avascular necrosis rates are related mainly to the time to surgery and surgical technique. Urgent reduction and fixation, within 24 hours from the onset of symptoms, was devised to restore capital blood flow to avoid AVN [11,15,16].

The results of the current meta-analysis did not indicate a statistically significant association between the AVN rates and time to surgery. Although the pooled AVN rates were highest with surgery within the "unsafe window", between 24 hours to 7 days for both the total AVN and CR AVN analysis (42% and 54% respectively). Furthermore, the number of included studies with adequate data in the respective analyses were 6 out of 12 for the total unstable SCFE and 4 out of 7 in the CR group. On the other hand, the pooled AVN rates with surgery beyond the 7th day were lower than the rate with surgery ≤24 hours in the total AVN analysis (18% compared to 21% respectively) but not for the CR AVN analysis (29% compared to 21% respectively). The number of the included studies was similar to the 24 hours - 7 days subgroup. Lastly, the number of hips included in the subgroup ≤24 hours were 190 and 117 in the total and CR analyses compared to 53 and 31 for 24 hours - 7 days and 43 and 18 hips who had surgery >7 days.

There was evidence of heterogeneity amongst the studies with outliers seen in the studies by Kalogrianitis et al [3] and Loder et al [12] reporting the highest AVN rates of 50% in 16 patients and 47% in 30 patients respectively. Whereas, the study by Philips et al [5] reported a 0% AVN rate for 14 unstable SCFE. Furthermore, there was significant heterogeneity within the first 2 timeframe subgroups (≤24 hours and between 24 hours - 7 days) and the highest was in the "unsafe window" subgroup (63% and 73% for the total and CR analyses respectively). Minimal heterogeneity was found in the studies with patients who had surgery beyond day 7, however, the included unstable SCFE were small in number, 43 and 18 in the total AVN and CR analyses respectively. The significant within subgroup heterogeneity can be explained by the following; (1) the included studies had mixed treatment techniques in the total AVN analysis and (2) there are many other variables affecting the AVN rates with unstable SCFE treatment including age, race, preoperative slip angle (severity) and the initial prodromal symptoms [6,7,17–19]. The above accounts for the wide variability of AVN rates across studies which would be more than what is expected by random sampling errors.

Studies assessing factors related to AVN with unstable SCFE have a common shortcoming

which is usually the small sample size due to the rarity of the condition and the presence of many subgroups of different surgical techniques in addition to other surgical and patient related factors. One additional confounding factor which is overlooked in the SCFE literature is the accuracy of the definition of clinical physeal stability. Loder et al. [12] defined clinically unstable SCFE as when the patient cannot ambulate even with crutches. In an interesting study by Ziebarth et al. [20], the authors assessed the correlation between Loder's definition of clinical stability and intraoperative physeal disruption. The sensitivity and specificity of Loder's stability classification was 39% and 76% respectively when compared to intraoperative findings. Thirteen out of 24 (54%) of the hips which were classified pre-operatively as Loder unstable SCFE had intraoperative intact physis (the periosteum was intact and several deep chisel cuts were required to separate the epiphysis for capital realignment.

Other surgical factors that may affect the AVN rate with unstable SCFE are the reduction techniques, either closed reduction [6,16], anterior open reduction with or without subcapital osteotomy [14,19] or capital realignment using the modified Dunn procedure [9] and whether to decompress the intracapsular hepatoma with closed reductions [21]. Reported AVN rates following closed reduction of unstable SCFE vary remarkably in the literature from 13% to 57% [3,4]. Closed reduction might cause stretching of the retinacular blood vessels over a posterior femoral neck healing callus in acute on chronic SCFE leading to AVN [6,20]. Our meta-analysis did not investigate this association and the included studies did not report the results of gentle closed reduction and fixation of unstable SCFE. However, the pooled AVN rates of patients who had CR were similar to the total AVN rate (24% and 29% respectively) and reflective of the actual AVN rate with this technique [18].

Releasing the intra-capsular hematoma with CR of unstable SCFE is another surgical factor which should relieve the intracapsular tamponade compressing the retinacular vessels [21]. In a meta-analysis by Ibrahim et al. [8], the pooled AVN rates were in favour of hip decompression but again this was not statistically significant. Interestingly, if we consider the model of the intra-capsular femoral neck fracture and its similarity to unstable SCFE, there is mixed evidence that decompression of the intra-capsular hematoma can decrease the AVN rate in femoral neck fractures [22,23]. Maruenda et al. [23] studied the effect of the intra-capsular hematoma on femoral head vascularity using 99mTc scintigraphy and found that decompressing the intra-capsular hematoma significantly decreased the intra-capsular pressure only in cases with impaired vascularity and low 99mTc uptake. However, there was no significant correlation between intra-capsular pressure and 99mTc scintigraphy ratio. They concluded that vascular damage related to the fracture is an important cause of avascular

necrosis despite the decreased femoral head vascularity by the intra-capsular tamponade effect. This is in agreement with the current view of the cause of AVN with unstable SCFE according to the intraoperative pathological findings with surgical hip dislocation [10].

The limitations of the current meta-analysis include the small number of included studies with the resultant limited number of patients included in the analysis. There were only twelve eligible published studies, but we chose to perform the meta-analysis to provide more generalizable results on the effect estimate. The only outcome measure examined in this meta-analysis was the rate of AVN. This is a clinically relevant and important outcome and the definition of AVN was the same amongst the twelve studies. Other important factors, such as the role of reduction, the type of fixation and post-operative management could not be controlled for in the analysis and require further study. This is common in studies reporting the results of treatment of unstable SCFE and the rarity of the condition. Furthermore, the mixed surgical techniques in the included studies with the variable treatment protocols and preoperative management including traction might further affect the AVN rates and cannot be accounted for. All the included studies were retrospective studies with the known disadvantages of recall bias.

Our study has only assessed the effect of time to surgery on the rate of AVN for unstable SCFE, which is one of many factors that may influence AVN. Hence, the cumulative evidence at present does not indicate a statistically significant association between time to surgery and a lower rate of AVN for unstable SCFE. However, orthopaedic surgeons may opt to avoid the "unsafe window" to optimize the blood flow to the femoral head. The results of our meta-analysis are based on observational studies, and thus, further attention should be directed to studies of good methodological quality. Therefore, multicentre prospective cohort studies are required with well-defined time to surgery outcomes.

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Figures & Tables

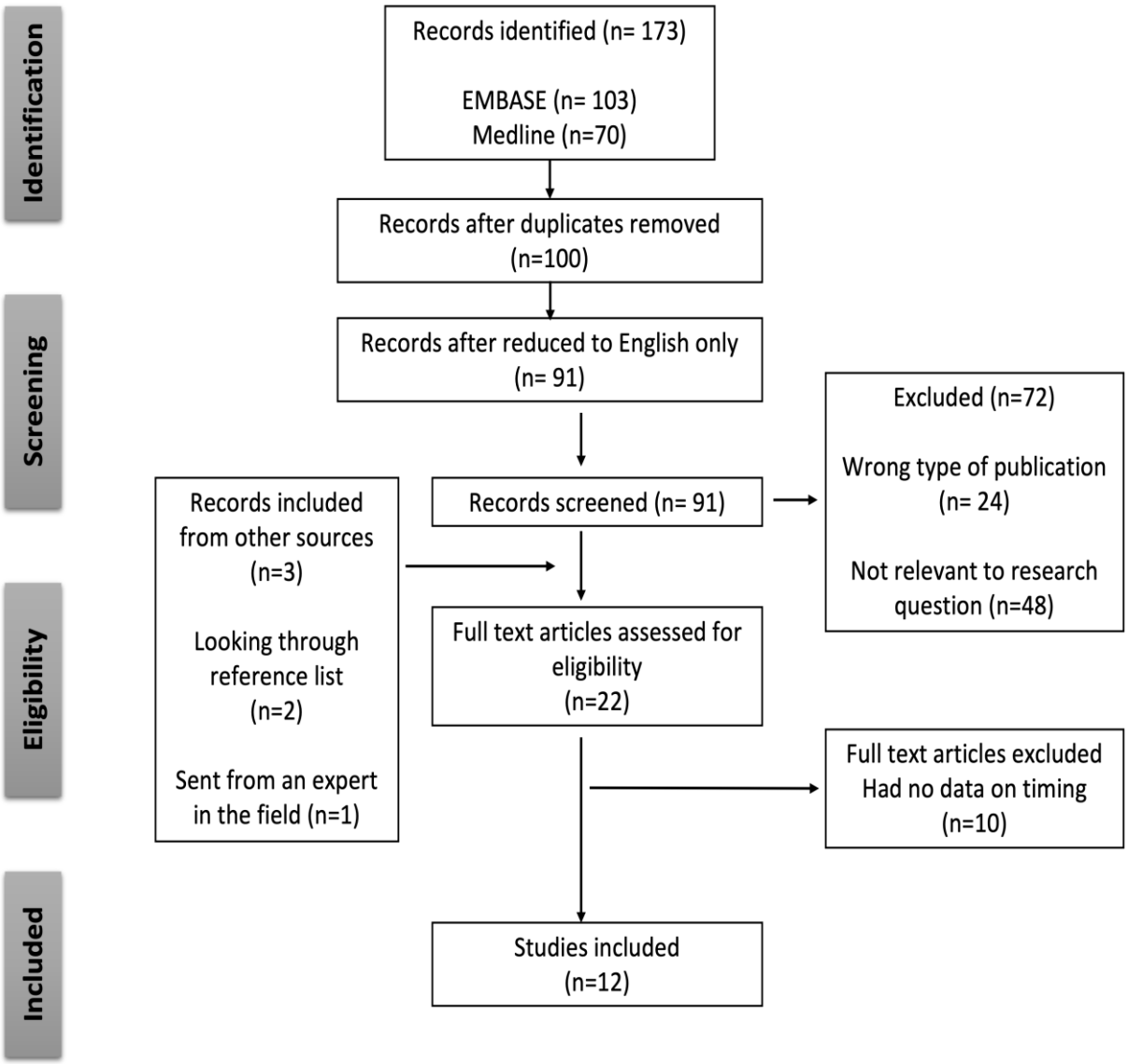

Figure 1: The flow chart of our study search results.

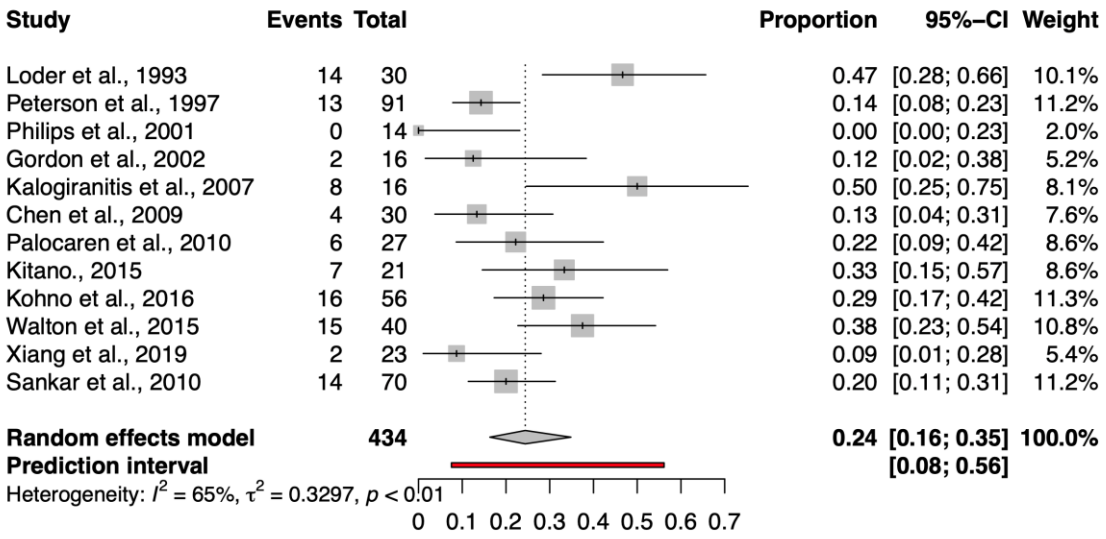

Figure 2: Forest plot of the pooled AVN rates for the total AVN analysis.

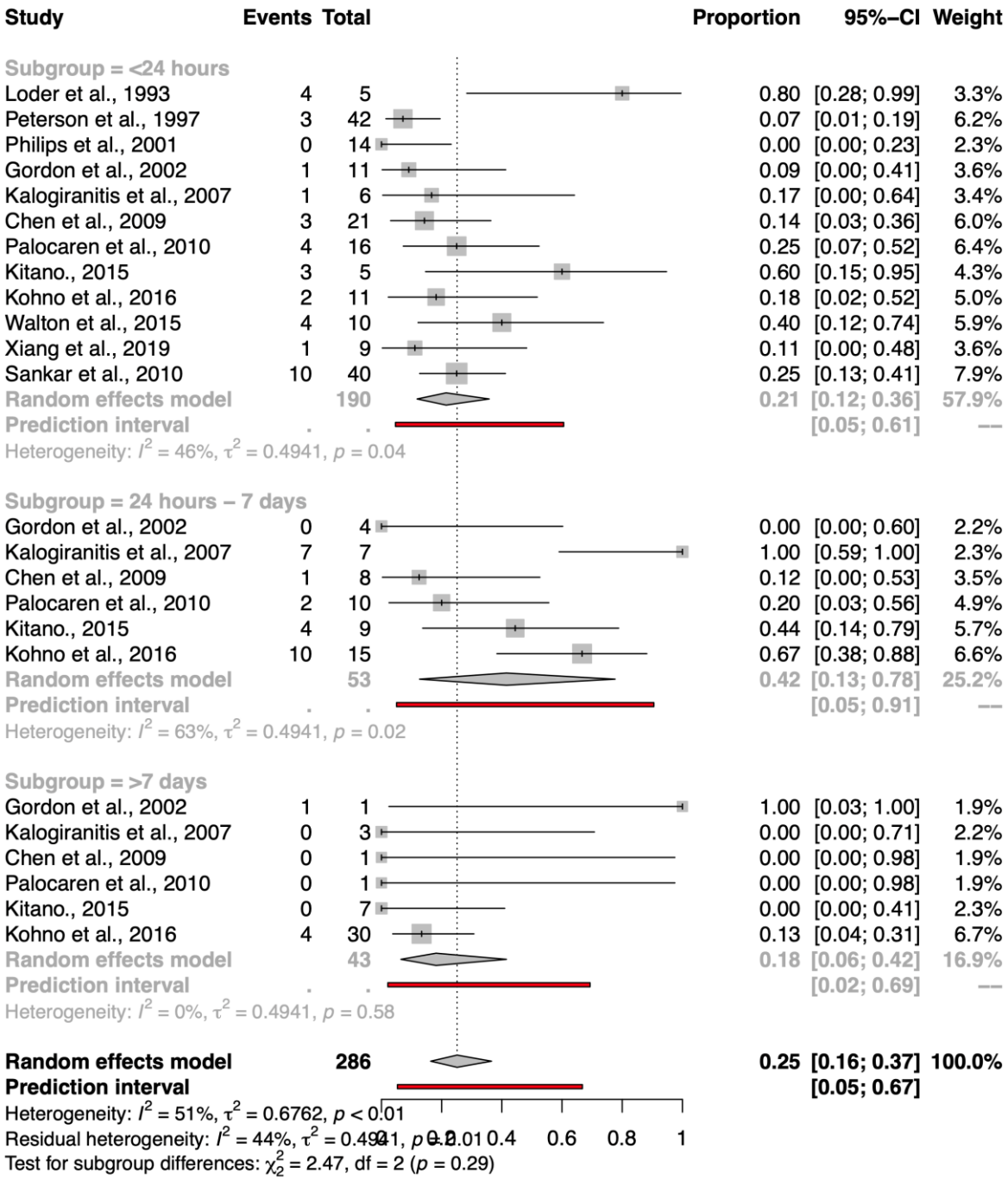

Figure 3: Forest plot pooled of the AVN rates for the total AVN analysis subgrouped according to time to surgery; ≤24 hours, 24 hours - 7 days and >7 days.

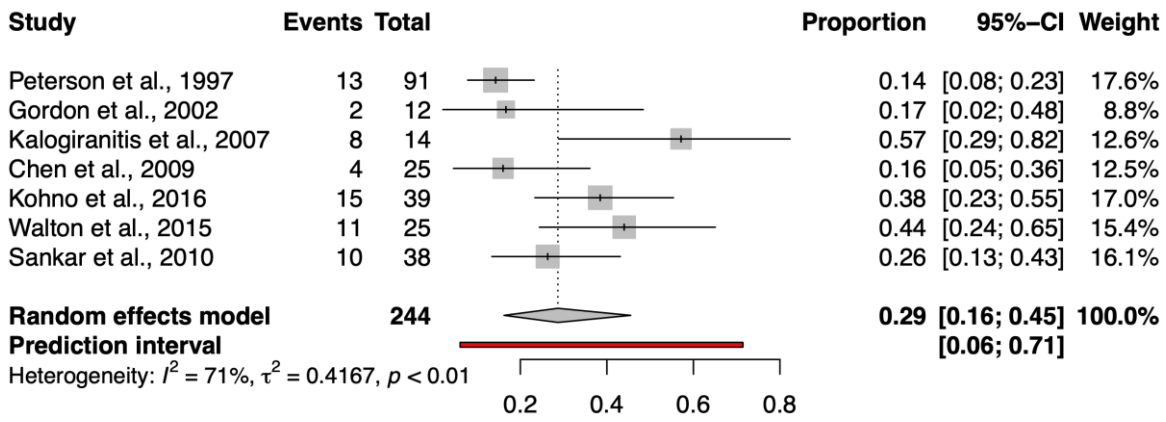

Figure 4: Forest plot of the pooled AVN rates for the CR AVN analysis.

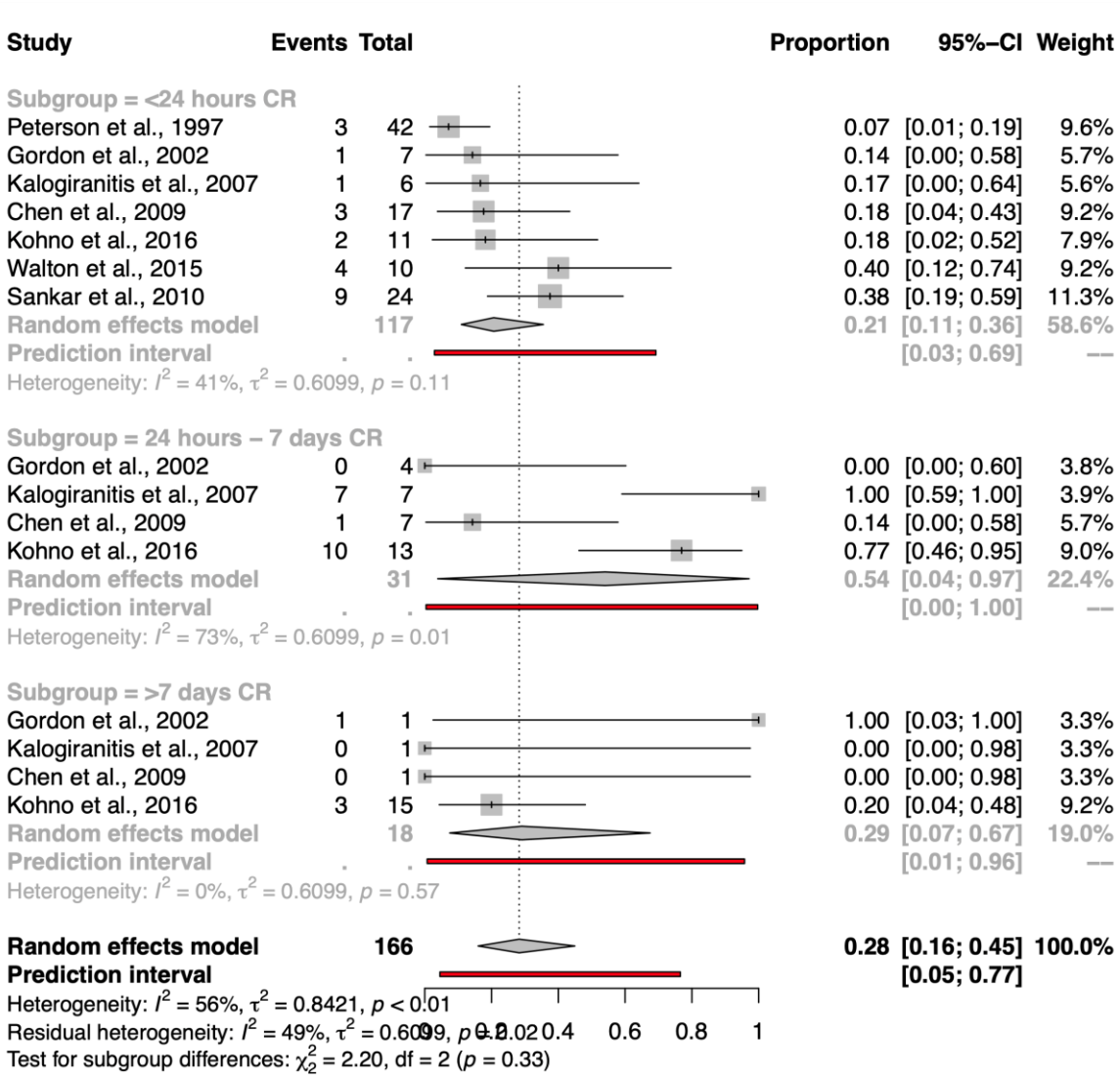

Figure 5: Forest plot of the pooled AVN rates for the CR AVN analysis subgrouped according to timing to surgery; ≤24 hours, 24 hours - 7 days and >7 days.

Table 1: Studies included in the meta-analysis. PIS: Pinning in situ, CR: Closed reduction, OR +/- Ost: Open reduction +/- sub capital osteotomy, SHD: Surgical hip dislocation.

Study	**Total no unstable slips**	**Total AVN no**	**PIS**	**CR**	**OR +/- Ost**	**SHD**	**Total ANV rate**	**<24 hr CR(Total)**	**>24 hr CR(Total)**	**24 hr - 7 days CR(Total)**	**> 7 days CR(Total)**
Loder eta al. 1993 [12]	30	14	4	24	2		0.47	(5)	(25)		
Petersen et al. 1997 [24]	91	13		91			0.14	42(42)	49 (49)		
Philips et al. 2001 [5]	14	0		14			0.00	(14)			
Gordon et al. 2002 [15]	16	2		12	4		0.13	7(11)	5 (5)	4(4)	1(1)
Kalogrianitis et al. 2007 [3]	16	8		14	2		0.50	6(6)	8 (10)	7(7)	1(3)
Chen et al. 2009 [11]	30	4		25	5		0.13	17(21)	8 (9)	7(8)	1(1)
Palocaren et al. 2010 [17]	27	6	25	2			0.22	(16)	(11)	(10)	(1)
Kitano et al. 2015 [6]	21	7	7	14			0.33	(5)	(16)	(9)	(7)
Kohno et al. 2016 [7]	56	16	17	39			0.29	11(11)	28 (45)	13(15)	15(30)
Walton et al. 2015 [19]	40	15		25	15		0.38	10(10)	15 (30)		
Xiang et al. 2019 [25]	23	2	18	5			0.09	(9)	5(14)	5(14)	
Sankar et al. 2010 [18]	70	14	16	38	8	8	0.20	40(40)	14 (30)		
Total	434	101	87	303	36	8	Avg 0.24				

Table 2: Assessment of the quality of the studies included in the meta-analysis (Newcastle-Ottawa scale)

Domain	Item	**Kalogrianitis et al.** [3]	**Palocaren et al.** [17]	**Kitano et al.** [6]	**Kohno et al.** [7]	**Walton et al.** [19]
Selection (4 stars)	Representativeness of the exposed cohort	*	*	*	*	*
	Selection of the unexposed cohort	*	*	*	*	*
	Ascertainment of exposure	*	*	*	*	*
	Demonstration that outcome of Interest was not present at start of study	*	*	*	*	*
Comparability (2 stars)	Comparability of cohorts on the basis of the design or analysis	*	**	**	*	*
Outcome (3 stars)	Assessment of outcome	*	*	*	*	*
	Was follow-up long enough for outcome to occur?	*	*	*	*	*
	Adequacy of follow-up of cohorts	*	*	*	*	*

Maximum number of stars is 9 for the three domains