



Systematic Review

Comparison of Postoperative Serum Biomarkers after Total Hip Arthroplasty through Minimally Invasive versus Conventional Approaches: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Nikolai Ramadanov ^{1,*}, Polina Marinova-Kichikova ², Robert Hable ³, Dobromir Dimitrov ⁴ and Roland Becker ¹

- Center of Orthopaedics and Traumatology, Brandenburg Medical School, University Hospital Brandenburg an der Havel, 14770 Brandenburg an der Havel, Germany; roland.becker@mhb-fontane.de
- Department of Surgical Propaedeutics, Faculty of Medicine, Medical University of Pleven, 5800 Pleven, Bulgaria; polina_g.marinova@abv.bg
- ³ Faculty of Applied Computer Science, Deggendorf Institute of Technology, 94469 Deggendorf, Germany; robert.hable@th-deg.de
- Department of Surgical Diseases, Faculty of Medicine, Medical University of Pleven, 5800 Pleven, Bulgaria; dobri_dimitrov@abv.bg
- * Correspondence: nikolai.ramadanov@gmail.com; Tel.: +49-177-740-66-33

Abstract: Background: An effective way to objectively assess intraoperative tissue damage in total hip arthroplasty (THA) is to determine and compare postoperative serum biomarkers (laboratory parameters) such as creatine kinase (CK), C-reactive protein (CRP), and hemoglobin (Hb). This meta-analysis aims to compare the intraoperative tissue damage in THA through minimally invasive (MI) and conventional approaches (CAs) using postoperative serum biomarkers. Methods: We searched databases for randomized controlled trials (RCTs) comparing MI THA and CA THA. We calculated mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes, using the Hartung-Knapp-Sidik-Jonkman method and a common effect/random effects model. Results: A total of 13 RCTs, involving 1186 THA patients, were included in our meta-analysis. In two out of eleven examined outcome parameters, MI THA showed better results than CA THA. In nine out of eleven examined outcome parameters, MI THA showed no significant difference compared to CA THA. MI THA had a 16 mg/L lower CRP value 3 days postoperatively than CA THA ($I^2 = 66\%$, p = 0.03, MD = -15.65, 95% CI -30.10 to -1.21). MI THA had a 3 mg/L lower CRP value 4 days postoperatively than CA THA ($I^2 = 0\%$, p = 0.98, MD = -3.00, 95% CI -3.27 to -2.74). Conclusions: Overall, there was no significant difference between MI THA and CA THA in terms of postoperative serum biomarkers, with a slight advantage of MI THA in CRP values. These results do not provide sufficient evidence to recommend changing the surgical approach from CA THA to MI THA. Level of evidence I: a systematic review of all relevant randomized controlled trials.

Keywords: minimally invasive; total hip arthroplasty; conventional approach; surgical approach; hip replacement; serum biomarkers



Citation: Ramadanov, N.;
Marinova-Kichikova, P.; Hable, R.;
Dimitrov, D.; Becker, R. Comparison
of Postoperative Serum Biomarkers
after Total Hip Arthroplasty through
Minimally Invasive versus
Conventional Approaches: A
Systematic Review and
Meta-Analysis of Randomized
Controlled Trials. *Prosthesis* 2023, 5,
694–710. https://doi.org/10.3390/
prosthesis5030049

Academic Editors: Giuseppe Solarino and Umberto Cottino

Received: 25 June 2023 Revised: 13 July 2023 Accepted: 20 July 2023 Published: 29 July 2023



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1. Introduction

Total hip arthroplasty (THA) is a promising solution for the treatment of many hip conditions such as osteoarthritis, femoral neck fracture, dysplasia, and avascular necrosis of the femoral head (ANFH) [1–3]. According to the anatomical relationship to the greater trochanter, there are six surgical approaches to the hip joint: anterior, anterolateral, direct lateral (transgluteal or transtrochanteric), posterior, posterolateral, and superior [4]. In an attempt to improve treatment outcomes, minimally invasive (MI) THA has been introduced and further developed over the past two decades. MI surgical approaches to the hip joint

are modifications of the well-known conventional approaches (CAs) that must meet two conditions: an incision length ≤ 10 cm and, most importantly, the preservation of muscles and tendons. The assumption that MI approaches would lead to a significantly better patient outcome due to less tissue damage is something that still needs to be scientifically proven [5-9]. A simple and effective way to objectively assess intraoperative tissue damage is to determine and compare postoperative serum biomarkers (laboratory parameters) such as creatine kinase (CK), C-reactive protein (CRP), and hemoglobin (Hb). CK is one of the important blood proteins that are produced by the breakdown of muscle fibers. It, therefore, serves as one of the most commonly used indirect markers of intraoperative muscle damage in humans [10]. CRP is another blood protein that is produced in the liver. It is the most important blood laboratory value for detecting and monitoring inflammation in humans [11]. The connection between tissue damage and inflammation is well-known [12], which is why CRP can be used to indirectly assess intraoperative tissue damage [11]. Another way to estimate intraoperative tissue damage is to measure the blood loss. The overall blood loss can be determined very reliably using the hemoglobin value, since its determination allows conclusions to be drawn about the hidden blood loss, whereas measuring the amount of intraoperative blood loss and the postoperative drainage directly only reveals a share of the overall blood loss [13]. Despite the long-standing use of MI approaches in THA, there is no meta-analysis in the literature examining differences in postoperative serum biomarkers between MI and CAs. One recently published systematic review of the literature by Sarantis et al. provided important findings on this topic, but without performing a meta-analysis of the extracted data [14]. There is a need for an objective assessment of the extent of intraoperative tissue damage in THA between MI approaches and CAs using postoperative serum biomarkers. The aim of this study is to confirm or refute the hypothesis that the extent of intraoperative tissue damage in THA through MI approaches, as measured by postoperative serum biomarkers, is less than in THA through CAs.

We formulated the following PICO (Population, Intervention, Control, and Outcomes) question: In human participants with hip conditions such as osteoarthritis, femoral neck fracture, dysplasia, and ANFH is MI THA superior to CA THA in terms of postoperative serum markers (CK, CRP, and Hb)?

2. Materials and Methods

2.1. Data Sources and Search Strategies

We registered our study protocol in PROSPERO on 10 August 2022 (CRD42022350279). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. The PRISMA checklist is available in Table S1 in the supplementary materials. The author group of the present study has certain experience in the field of meta-analyses and THAs. For this reason, the methods described in some publications [16–19] of this author group are similar or partially identical to the present meta-analysis. We searched the following databases and checked citations of the related meta-analyses for relevant manuscripts up to 31 March 2023: PubMed, CNKI, The Cochrane Library, Clinical Trials, CINAHL, and Embase. We built a BOOLEAN search strategy, adapted to the syntax of the used databases. No restrictions to publication language were applied. Since there are constant advances in THA, especially for MI surgical techniques, we decided not to include old studies published before 2010.

2.2. Study Screening and Selection

First, we examined the titles, then the abstracts, and finally the full texts of the articles. The decision on the inclusion of each study was made by the consensus between two reviewers (NR, PMK). We used the Kappa coefficient to measure the agreement between them. Disagreements were resolved by scientific discussion.

2.3. Inclusion Criteria

Types of studies:

• randomized controlled trials (RCTs).

Types of participants:

 human participants with hip conditions such as osteoarthritis, femoral neck fracture, dysplasia, and ANFH.

Types of interventions:

• MI THA or CA THA.

MI THA definition: In our meta-analysis, an approach was defined as MI if the approach per se is known as MI in the literature or if the approach was explicitly referred to as MI in the individual RCTs.

Types of outcome measures (postoperative serum biomarkers, laboratory parameters):

- creatine kinase (CK);
- C-reactive protein (CRP);
- hemoglobin (Hb).

2.4. Statistical Analysis

2.4.1. Data Extraction and Quality Assessment

Two reviewers (NR, PMK) independently extracted all relevant data on RCT characteristics, methods, quality assessment, characteristics of participants, details of the interventions, relevant outcomes, and relevant additional information. Disagreements were resolved by scientific discussion. The extracted data are available in Excel S1 in the supplementary materials. We performed a risk of bias assessment according to Cochrane's Risk of Bias 2 (RoB 2) tool [20] and a level of evidence assessment according to the recommendations of the GRADE system [21]. In addition, we assessed publication bias using Begg's and Egger's tests.

The RoB 2 tool can be used to estimate the likelihood that study design features cause misleading results [20]. After considering all quality aspects, an overall rating of "low risk", "moderate risk", or "high risk" is made for each study [20]. The results of a "low risk" study are considered valid, while the results of a "high risk" study might be considered invalid [20].

GRADE is a tool that allows assessment of the quality of evidence, using four levels of evidence: "very low", "low", "moderate", and "high" [21]. The evidence levels indicate to what extent the true effect deviates from the estimated effect [21]. Since the quality of the evidence often varies between the outcome parameters, it is determined individually for each endpoint [21].

The publication bias indicates a statistical distortion of the data presentation in scientific journals, which can occur as a result of a preferred publication of studies with "positive" or significant results.

2.4.2. Measures of Treatment Effect

We calculated mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes, using the Hartung–Knapp–Sidik–Jonkman method and a common effect/random effects model. The Hartung–Knapp–Sidik–Jonkman method is a simple and robust approach to meta-analysis that is gaining more popularity among statisticians. It far surpasses the standard method of DerSimonian-Laird [22]. Common effect (or fixed effects) and random effects models are statistical models, both of which are regularly used in meta-analyses. A common effect model assumes only one true effect, which can be disadvantageous if there is considerable heterogeneity between the primary studies. A random effects model assumes that the actual effect may vary due to heterogeneity within the studies examined [23]. We performed study weighting by inverse variance. We calculated the t-test to determine the differences between the means of the two groups. We

assessed heterogeneity using Cochrane's Q test (*p*-value < 10 is indicative of heterogeneity) and Higgins test I² (low heterogeneity: <25%, moderate heterogeneity: 25–75%, and high heterogeneity: >75%) [24]. As these values indicated a high amount of heterogeneity for some parameters, we adhered to the random effects model in our result presentation. Taking measurement accuracy into account, the results are reported with two decimal places. All statistic calculations were performed using the R packages meta and metafor.

2.4.3. Missing Data

We contacted the authors of the RCTs for missing data. If relevant data were still missing, the RCT was excluded to ensure the high-quality inclusion of RCTs. If the information on standard deviation (SD) was missing, it was calculated via imputation [25]. In case the RCTs provided different information on intention to treat (ITT) and per protocol (PP) analysis, we used the numbers from the ITT analysis.

3. Results

Our initial literature search identified 6908 records. After the subtraction of 2457 duplicates, the title and abstract of 4451 records were independently screened by two reviewers (NR and PMK). After the exclusion of 4406 records, 45 articles ($\kappa = 0.98$) were screened by full-text analysis [26–70]. Of those 45 articles, 32 (κ = 1.00) were excluded due to missing relevant outcome parameters [26-57]. A total of 13 RCTs [58-70] with 1186 THA patients were included in the final meta-analysis. The study selection process is presented in a flowchart (Figure 1). The main characteristics of the included RCTs are listed in Table 1. Of the 1186 THA patients, 491 (41.40%) were male. The mean age of the patient cohort was 71.23 years. The mean body mass index (BMI) of the patient cohort was 28.62 kg/m². The risk of bias and level of evidence assessments are presented in Tables 2 and 3, respectively. Two [62,69] out of thirteen RCTs [58-70] showed a high risk of bias, seven [58,59,61,63,64,66,68] out of thirteen RCTs [58–70] showed a moderate risk of bias, and four [60,65,67,70] out of thirteen RCTs [58–70] showed a low risk of bias. Six (CK 2–4 days postoperatively, CRP 1 and 2 days postoperatively, and Hb 1 day postoperatively) out of eleven outcome parameters showed a low level of evidence, four (CK 1 day postoperatively, CRP 3 and 4 days postoperatively, and Hb 2 days postoperatively) out of eleven outcome parameters showed a moderate level of evidence, and one (Hb 3 days postoperatively) out of eleven outcome parameters showed a high level of evidence. The publication bias evaluation, using Begg's and Egger's tests, is presented in Table 4. Only one (Hb 1 day postoperatively) out of eleven outcome parameters showed a significant publication bias. No clinical heterogeneity was detected when comparing the clinical characteristics for gender, age, and BMI (Table 1) between the MI THA and CA THA groups. The statistical heterogeneity of all measured outcomes is shown in Figures 2–12. Table 5 shows the weighted mean values of the postoperative serum biomarkers.

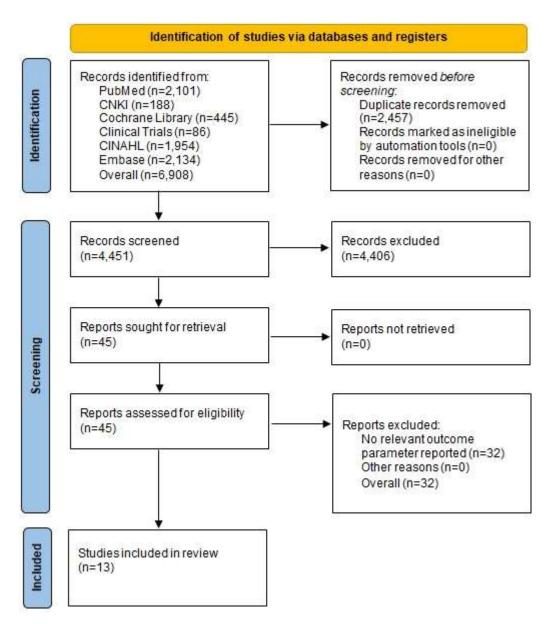


Figure 1. PRISMA flow diagram of the search results and selection process.

Table 1. Main characteristics of RCTs [58–70].

RCT	Year of Publication, Origin	Patients, N	Gender, Male, N	Approach	THA with Bone Cement, N	Patient Position on Table	Mean Age, Years, SD	Mean BMI, kg/m², SD	HHS Preoperatively, Points	Osteoarthritis, N	Femoral Neck Fracture, N	Dysplasia, N	ANFH, N
De Anta-Diaz	2016, Spain	49	26	MI DAA	8	NR	64.80 ± 10.10	26.60 ± 3.90	44.40 ± 13.60	49	0	0	0
et al. [58]	, , ,	50	26	CA L	6	NR	63.50 ± 12.50	26.90 ± 3.10	42.90 ± 15.20	50	0	0	0
		42	14	MI MH	2	Lat	61.00 ± 13.00	26.10 ± 3.00	48.00 ± 15.00	42	0	0	0
Dienstknecht et al. [59] *	2013, Germany	36	12	CA L	1	NR	62.00 ± 13.00	24.30 ± 3.60	46.00 ± 16.00	36	0	0	0
[2.7]	,	41	24	MI MH	3	Lat	61.00 ± 11.00	34.30 ± 4.40	44.00 ± 15.00	41	0	0	0
		15	10	CA L	0	NR	61.00 ± 10.00	34.60 ± 4.10	46.00 ± 16.00	15	0	0	0
Khan et al.	2012,	44	24	MI P	44	Lat	72.30 ± 1.00	28.50 ± 0.70	NR	42	0	0	2
[60]	Australia	45	19	CA P	45	Lat	72.80 ± 1.10	28.90 ± 0.60	NR	43	0	0	2
Landgraeber	2013,	36	12	MI AL	36	Lat	70.26 ± 4.05	27.03 ± 2.82	NR	36	0	0	0
et al. [61]	Germany	40	14	CA L	40	Supine	71.03 ± 5.38	26.75 ± 3.83	NR	40	0	0	0
Li [62]	2020, China .	30	16	MI S	NR	Lat	70.35 ± 4.26	NR	25.41 ± 2.41	NR	NR	NR	NR
En [OZ]		30	18	CA PL	NR	Lat	70.12 ± 4.78	NR	26.35 ± 2.47	NR	NR	NR	NR
Li et al. [63]	2021, China	49	27	MI S	NR	Lat	75.53 ± 7.34	22.99 ± 2.87	NR	0	15	0	34
Er et al. [00]		47	24	CA PL	NR	Lat	77.21 ± 7.84	22.70 ± 3.00	NR	0	16	0	31
Martin et al.	2011,	42	12	MI AL	42	Lat	66.70 ± 10.10	30.60 ± 6.10	37.40 ± 15.50	37	0	0	5
[64]	Belgium	41	14	CA L	41	NR	63.10 ± 10.20	29.40 ± 5.50	40.20 ± 12.90	37	0	0	4
Mjaaland	2015, Norway	83	25	MI DAA	83	Supine	67.20 ± 8.60	27.70 ± 3.60	53.60 ± 13.70	83	0	0	0
et al. [65]		80	30	CA L	80	Lat	65.60 ± 8.60	27.60 ± 3.90	56.00 ± 11.20	80	0	0	0
Nistor et al.	2017,	35	26	MI DAA	0	Supine	67.00 ± 4.75	27.45 ± 3.76	NR	35	0	0	0
[66]	Romania	35	16	CA L	0	Supine	64.00 ± 3.25	28.63 ± 3.12	NR	35	0	0	0
Ouyang et al. [67]	2018, China .	12	8	MI S	NR	Lat	54.00 ± 6.50	23.10 ± 2.30	45.67 ± 5.93	5	0	0	7
[67]	2010, China	12	9	CA PL	NR	Lat	55.00 ± 5.00	23.90 ± 3.40	46.92 ± 8.94	6	0	0	6
Rykov et al.	2017,	23	8	MI DAA	23	Supine	62.80 ± 6.10	29.00 ± 5.60	52.00 ± 6.67	23	0	0	0
[68]	Netherlands	23	11	CA PL	23	Lat	60.20 ± 8.10	29.30 ± 4.80	51.00 ± 8.95	23	0	0	0
Varela-	2013, Spain	25	12	MI L	0	NR	64.80 ± 10.50	28.27 ± 3.67	52.70 ± 12.92	21	0	0	4
Egocheaga et al. [69]		25	12	CA L	0	NR	63.80 ± 9.70	27.78 ± 3.24	51.30 ± 14.94	22	0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	3
Xiao et al.	2021, China .	49	16	MI P	0	Lat	71.06 ± 10.87	26.73 ± 4.18	NR	0	49	0	0
[70]	2021, Cinia .	57	26	CA PL	0	Lat	73.93 ± 10.02	26.39 ± 4.64	NR	0	57	0	0

MI: minimally invasive; AL: anterolateral; DAA: direct anterior approach; L: lateral; MH: MicroHip; P: posterior; PL: posteriolateral; S: SuperPATH; CA: conventional approach; Lat: lateral decubitus position; THA: total hip arthroplasty; BMI: Body Mass Index; HHS: Harris Hip Score; ANFH: avascular necrosis of the femoral head; NR: not reported; SD: standard deviation; RCT: randomized controlled trial; * This RCT divided the patient cohort according to their BMI.

Table 2. Risk of bias assessment [58–70].

Study	Bias Arising from the Randomization Process	Bias Due to Deviation from Intended Interventions	Bias Due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Result	Overall Risk of Bias
De Anta-Diaz et al. [58]	-	+	+	+	+	?
Dienstknecht et al. [59]	-	+	+	+	+	?
Khan et al. [60]	+	+	+	+	+	+
Landgraeber et al. [61]	+	?	+	+	?	?
Li [62]	+	?	-	-	+	-
Li et al. [63]	+	+	-	+	+	?
Martin et al. [64]	?	?	+	+	?	?
Mjaaland et al. [65]	+	+	+	+	+	+
Nistor et al. [66]	-	+	+	+	+	?
Ouyang et al. [67]	+	+	+	+	+	+
Rykov et al. [68]	+	+	-	+	+	?
Varela-Egocheaga et al. [69]	-	-	+	+	+	-
Xiao et al. [70]	?	+	+	+	+	+

(+): low risk of bias; (?): some concerns; (-): high risk of bias.

Table 3. Level of evidence assessment according to GRADE recommendations.

No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality of Evidence			
			1. 0	CK 1 day postoperatively						
6	RCT	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	-	Moderate			
2. CK 2 days postoperatively										
3	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
			3. C	CK 3 days postoperatively						
5	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
4. CK 4 days postoperatively										
3	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
5. CRP 1 day postoperatively										
5	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
			6. C	RP 2 days postoperatively						
6	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
			7. C.	RP 3 days postoperatively						
4	RCT	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	-	Moderate			
			8. C	RP 4 days postoperatively						
2	RCT	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	-	Moderate			
			9. I	Hb 1 day postoperatively						
7	RCT	Moderate	Serious	No serious indirectness	No serious imprecision	-	Low			
			10. I	Hb 2 days postoperatively	-					
5	RCT	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	-	Moderate			
			11. I	Hb 3 days postoperatively						
3	RCT	Low	No serious inconsistency	No serious indirectness	No serious imprecision	-	High			

 $RCT: randomized \ controlled \ trial; CK: creatine \ kinase; CRP: C-reactive \ protein; Hb: \ hemoglobin.$

Table 4. Publication bias evaluation.

	Number of RCTs	Egger <i>p-</i> Value	Begg <i>p-</i> Value
1. CK 1 day postoperatively	6	0.75	1.00
2. CK 2 days postoperatively	3	0.76	1.00
3. CK 3 days postoperatively	5	0.37	1.00
4. CK 4 days postoperatively	3	0.70	1.00
5. CRP 1 day postoperatively	5	0.76	0.81
6. CRP 2 days postoperatively	6	0.44	0.26
7. CRP 3 days postoperatively	4	0.46	0.73
8. CRP 4 days postoperatively	2	-	-
9. Hb 1 day postoperatively	7	0.04 *	0.23
10. Hb 2 days postoperatively	5	0.26	0.22
11. Hb 3 days postoperatively	3	0.42	1.00

CK: creatine kinase; CRP: C-reactive protein; Hb: hemoglobin; * significant result.

Table 5. Summary of results showing the weighted mean values of the outcome parameters.

Postoperative Serum Biomarkers	MI THA	CA THA
1. CK 1 day postoperatively (in U/L)	543.61	597.12
2. CK 2 days postoperatively (in U/L)	649.69	661.28
3. CK 3 days postoperatively (in U/L)	686.92	732.59
4. CK 4 days postoperatively (in U/L)	587.48	499.72
5. CRP 1 day postoperatively (in mg/L)	29.33	34.61
6. CRP 2 days postoperatively (in mg/L)	65.62	56.01
7. CRP 3 days postoperatively (in mg/L)	60.11	74.79
8. CRP 4 days postoperatively (in mg/L)	23.63	26.32
9. Hb 1 day postoperatively (in g/dL)	11.01	11.01
10. Hb 2 days postoperatively (in g/dL)	10.73	10.72
11. Hb 3 days postoperatively (in g/dL)	10.34	10.38

CK: creatine kinase; CRP: C-reactive protein; Hb: hemoglobin; MI: minimally invasive; CA: conventional approach; THA: total hip arthroplasty.

Outcome parameters: postoperative serum biomarkers.

3.1. CK 1 Day Postoperatively: MI THA vs. CA THA

Data on 485 THAs were pooled from six RCTs ($I^2 = 90\%$, p < 0.01, Figure 2). The CK 1 day postoperatively of MI THA showed no significant difference compared to the CK 1 day postoperatively of CA THA (MD = -49.77, 95% CI -157.74 to 58.21).

3.2. CK 2 Days Postoperatively: MI THA vs. CA THA

Data on 332 THAs were pooled from three RCTs ($I^2 = 98\%$, p < 0.01, Figure 3). The CK 2 days postoperatively of MI THA showed no significant difference compared to the CK 2 days postoperatively of CA THA (MD = -17.49, 95% CI -403.84 to 368.87).

3.3. CK 3 Days Postoperatively: MI THA vs. CA THA

Data on 459 THAs were pooled from five RCTs ($I^2 = 98\%$, p < 0.01, Figure 4). The CK 3 days postoperatively of MI THA showed no significant difference compared to the CK 3 days postoperatively of CA THA (MD = -109.19, 95% CI -392.31 to 173.93).

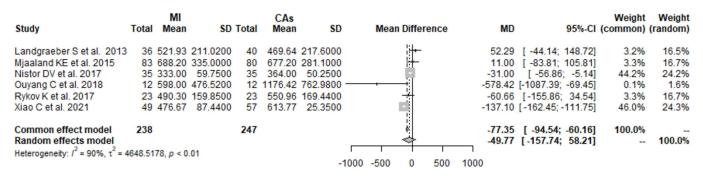


Figure 2. Comparison of the CK 1 day postoperatively (U/L). SD: standard deviation; MD: mean difference; CI: confidence interval [61,65–68,70].

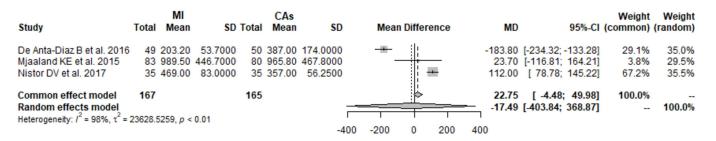


Figure 3. Comparison of the CK 2 days postoperatively (U/L). SD: standard deviation; MD: mean difference; CI: confidence interval [58,65,66].

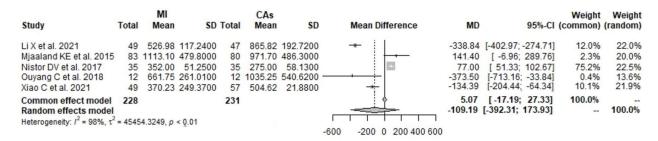


Figure 4. Comparison of the CK 3 days postoperatively (U/L). SD: standard deviation; MD: mean difference; CI: confidence interval [63,65-67,70].

3.4. CK 4 Days Postoperatively: MI THA vs. CA THA

Data on 332 THAs were pooled from three RCTs ($I^2 = 97\%$, p < 0.01, Figure 5). The CK 4 days postoperatively of MI THA showed no significant difference compared to the CK 4 days postoperatively of CA THA (MD = 39.81, 95% CI -296.91 to 376.52).

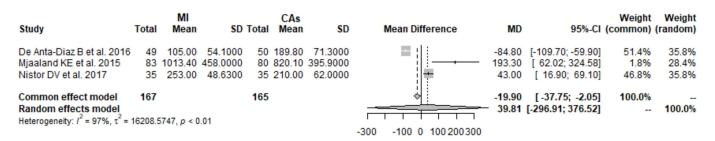


Figure 5. Comparison of the CK 4 days postoperatively (U/L). SD: standard deviation; MD: mean difference; CI: confidence interval [58,65,66].

3.5. CRP 1 Day Postoperatively: MI THA vs. CA THA

Data on 415 THAs were pooled from five RCTs ($I^2 = 66\%$, p = 0.02, Figure 6). The CRP 1 day postoperatively of MI THA showed no significant difference compared to the CRP 1 day postoperatively of CA THA (MD = -3.26, 95% CI -12.77 to 6.24).

Study	MI Total Mean SI	CAs) Total Mean SD	Mean Difference	MD 95%-CI	Weight Weight (common) (random)
Landgraeber S et al. 2013 Mjaaland KE et al. 2015 Ouyang C et al. 2018 Rykov K et al. 2017 Xiao C et al. 2021	36 9.94 0.4900 83 19.40 14.8000 12 51.01 27.3800 23 19.70 17.5500 49 59.51 26.2800	80 22.40 17.7000 12 67.79 22.4400 23 11.39 13.3800	+ + + + + + + + + + + + + + + + + + +	-2.49 [-3.80; -1.18] -3.00 [-8.02; 2.02] -16.78 [-36.81; 3.25] 8.31 [-0.71; 17.33] -10.19 [-17.59; -2.79]	89.0% 29.6% 6.0% 24.8% 0.4% 7.0% 1.9% 18.0% 2.8% 20.7%
Common effect model Random effects model Heterogeneity: I^2 = 66%, τ^2 = 3	203 31.6499, <i>p</i> = 0.02	212	-30 -20 -10 0 10 20 30	-2.59 [-3.82; -1.36] -3.26 [-12.77; 6.24]	100.0% 100.0%

Figure 6. Comparison of the CRP 1 day postoperatively (mg/L). SD: standard deviation; MD: mean difference; CI: confidence interval [61,65,67,68,70].

3.6. CRP 2 Days Postoperatively: MI THA vs. CA THA

Data on 644 THAs were pooled from six RCTs ($I^2 = 22\%$, p = 0.27, Figure 7). The CRP 2 days postoperatively of MI THA showed no significant difference compared to the CRP 2 days postoperatively of CA THA (MD = -1.97, 95% CI -4.65 to 0.71).

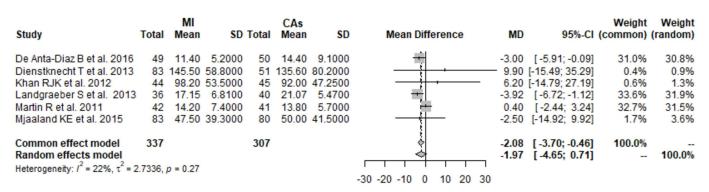


Figure 7. Comparison of the CRP 2 days postoperatively (mg/L). SD: standard deviation; MD: mean difference; CI: confidence interval [58–61,64,65].

3.7. CRP 3 Days Postoperatively: MI THA vs. CA THA

Data on 389 THAs were pooled from four RCTs ($I^2 = 66\%$, p = 0.03, Figure 8). The CRP 3 days postoperatively of MI THA was 15.7 mg/L lower than the CRP 3 days postoperatively of CA THA (MD = -15.65, 95% CI -30.10 to -1.21).

Study	MI Total Mean	SD Total Mea	(250)	Mean Difference	MD	Weight 95%-CI (common)	Weight (random)
Li X et al. 2021 Mjaaland KE et al. 2015 Ouyang C et al. 2018 Xiao C et al. 2021 Common effect model Random effects model Heterogeneity: I ² = 66%, τ ²	12 63.27 49.4 49 97.21 39.2 193	3000 80 51.6 4300 12 87.5 2700 57 113.2 196	5 12.9200 0 39.6000 5 38.9400 9 4.9800		-22.12 [-26.52; -3.20 [-15.32 -24.28 [-59.88; -16.08 [-27.15; -19.50 [-23.35; -15.65 [-30.10;	; 8.92] 10.1% 11.32] 1.2% ; -5.01] 12.1% -15.65] 100.0%	39.7% 26.0% 6.5% 27.8%

Figure 8. Comparison of the CRP 3 days postoperatively (mg/L). SD: standard deviation; MD: mean difference; CI: confidence interval [63,65,67,70].

3.8. CRP 4 Days Postoperatively: MI THA vs. CA THA

Data on 262 THAs were pooled from two RCTs ($I^2 = 0\%$, p = 0.98, Figure 9). The CRP 4 days postoperatively of MI THA was 3 mg/L lower than the CRP 4 days postoperatively of CA THA (MD = -3.00, 95% CI -3.27 to -2.74).

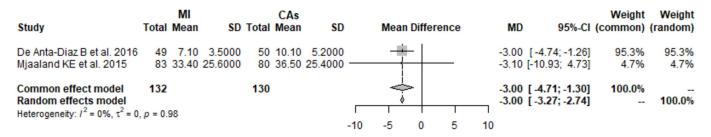


Figure 9. Comparison of the CRP 4 days postoperatively (mg/L). SD: standard deviation; MD: mean difference; CI: confidence interval [58,65].

3.9. Hb 1 Day Postoperatively: MI THA vs. CA THA

Data on 642 THAs were pooled from seven RCTs ($I^2 = 61\%$, p = 0.02, Figure 10). The Hb 1 day postoperatively of MI THA showed no significant difference compared to the Hb 1 day postoperatively of CA THA (MD = -0.02, 95% CI -0.40 to 0.36).

Study	MI Total Mean	CAs SD Total Mean		Mean Difference	MD 95%-CI	Weight Weight (common) (random)
Dienstknecht T et al. 2013 Khan RJK et al. 2012 Landgraeber S et al. 2013 Mjaaland KE et al. 2015 Ouyang C et al. 2018 Varela-Egocheaga JR et al. 2013 Xiao C et al. 2021	83 11.40 1. 44 10.37 1. 36 11.38 1. 83 11.10 1. 12 12.63 1. 25 10.68 1. 49 9.88 1.	9000 45 10.14 4800 40 11.33 2000 80 11.60 3900 12 12.28 4200 25 11.10	1.6300 1.4600 1.3000 0.5000		-0.30 [-0.84; 0.24] 0.23 [-0.51; 0.97] 0.05 [-0.61; 0.71] -0.50 [-0.88; -0.12] 0.35 [-0.49; 1.19] -0.42 [-1.36; 0.52] 0.47 [0.09; 0.85]	9.6% 13.2% 28.4% 20.1% 6.0% 10.1% 4.8% 8.7%
Common effect model Random effects model Heterogeneity: I^2 = 61%, τ^2 = 0.1069,	332 p = 0.02	310	-	1 -0.5 0 0.5 1	-0.03 [-0.23; 0.18] -0.02 [-0.40; 0.36]	

Figure 10. Comparison of the Hb 1 day postoperatively (mmol/L). SD: standard deviation; MD: mean difference; CI: confidence interval [59–61,65,67,69,70].

3.10. Hb 2 Days Postoperatively: MI THA vs. CA THA

Data on 506 THAs were pooled from five RCTs ($I^2 = 73\%$, p < 0.01, Figure 11). The Hb 2 days postoperatively of MI THA showed no significant difference compared to the Hb 2 days postoperatively of CA THA (MD = 0.02, 95% CI -0.67 to 0.72).

Study	MI Total Mean S	CAs D Total Mean SD	Mean Difference	MD 95%-CI	Weight Weight (common) (random)
Dienstknecht T et al. 2013 Landgraeber S et al. 2013 Martin R et al. 2011 Mjaaland KE et al. 2015 Varela-Egocheaga JR et al. 2013	83 10.80 1.600 36 11.25 1.350 42 10.40 1.500 83 10.90 1.300 3 25 9.56 1.250	0 40 10.80 1.4700 0 41 9.60 1.5000 0 80 11.30 1.2000		-0.50 [-1.06; 0.06] 0.45 [-0.18; 1.08] - 0.80 [0.15; 1.45] -0.40 [-0.78; -0.02] -0.09 [-0.82; 0.64]	14.8% 19.1% 14.3% 18.9% 40.5% 23.9%
Common effect model Random effects model Heterogeneity: I^2 = 73%, τ^2 = 0.2266,	269 p < 0.01	237	-1 -0.5 0 0.5 1	-0.09 [-0.33; 0.16] 0.02 [-0.67; 0.72]	100.0% 100.0%

Figure 11. Comparison of the Hb 2 days postoperatively (mmol/L). SD: standard deviation; MD: mean difference; CI: confidence interval [59,61,64,65,69].

3.11. Hb 3 Days Postoperatively: MI THA vs. CA THA

Data on 293 THAs were pooled from three RCTs ($I^2 = 85\%$, p < 0.01, Figure 12). The Hb 2 days postoperatively of MI THA showed no significant difference compared to the Hb 3 days postoperatively of CA THA (MD = 0.01, 95% CI -1.22 to 1.23).

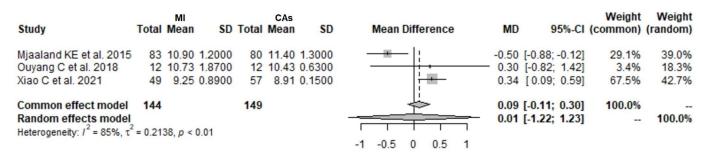


Figure 12. Comparison of the Hb 3 days postoperatively (mmol/L). SD: standard deviation; MD: mean difference; CI: confidence interval [65,67,70].

4. Discussion

Our literature search revealed 13 RCTs with 1186 THA patients which were included in the final meta-analysis. The extent of the included RCTs allowed us to examine three relevant postoperative serum biomarkers (CK, CRP, and Hb). In two out of eleven examined outcome parameters, MI THA showed significantly better results than CA THA. In nine out of eleven examined outcome parameters, MI THA showed no significant difference compared to CA THA. Taking the examined outcome parameters into account, we allow ourselves to state that MI THA and CA THA show overall no significant difference in terms of postoperative serum biomarkers, with a slight advantage of MI THA in CRP values. Therefore, these differences do not justify changing the operative approach based on the examined outcome parameters. The choice of the operative approach still should be left to the experience and preference of the operating surgeon.

We examined CK and CRP on postoperative days 1–4 and Hb on postoperative days 1–3. The combination of the 11 examined outcome parameters provides an objective impression of the extent of intraoperative tissue damage in THA. Figures 2–12 show that MI THA had statistically better results or no significant difference in postoperative serum biomarkers compared to CA THA. MI THA had a 16 mg/L lower CRP value 3 days postoperatively than CA THA. MI THA had a 3 mg/L lower CRP value 4 days postoperatively than CA THA. When interpreting statistically significant differences, the question of clinical relevance is crucial. Minimal clinically important differences (MCIDs) are patient-derived scores that justify changes in a clinical intervention. Although the literature does not provide any information on specific values for the examined postoperative serum biomarkers (CK, CRP, and Hb) in THA, the statistically significant differences do not seem to reach MCID at first appearance.

Our meta-results are similar to the findings of the recently published systematic review on this topic [14]. The study of Sarantis et al., including 31 studies, found no relevant differences between THA approaches when evaluating biomarkers (CK, CRP, myoglobin, erythrocyte sedimentation rate, skeletal troponin, and interleukins) [14]. Only a slight advantage of anterior and minimally invasive approaches was noted [14].

There are some strengths of this meta-analysis that need to be highlighted. To the best of our knowledge, this is the first systematic review and meta-analysis examining differences in postoperative serum biomarkers between MI THA and CA THA. In our meta-analysis, we applied high-quality statistical methods. The literature search was limited to RCTs to obtain more reliable meta-results. The RCT quality was determined by assessment of the risk of bias, the level of evidence, and the publication bias. Two statistical models, namely the common effect and the random effects models, were calculated. Fur-

thermore, the Hartung–Knapp–Sidik–Jonkman method was used instead of the standard DerSimonian-Laird method, which is recommended in the recent literature [22].

In day-by-day clinical work, the main findings of this meta-analysis give important insight for orthopedic surgeons. The knowledge that the postoperative serum biomarkers of MI THA and CA THA do not differ relevantly could help orthopedic surgeons choose their surgical approach and operational technique. Furthermore, the calculated weighted mean values of the postoperative serum biomarkers CK, CRP, and Hb represent a reliable reference value that can be compared to the postoperative laboratory values after THA in other hospitals for critical self-control.

We identified the following limitations to our meta-analysis. (1) Significant heterogeneity was detected between the included RCTs for several outcome parameters. (2) The included studies summarized different surgical indications in a meta-analysis: osteoarthritis, femoral neck fracture, dysplasia, and ANFH. (3) In some outcome parameters, the sample size and the number of RCTs included were small. (4) The follow-up period of 4 days in our meta-analysis is relatively short. However, the short follow-up period results from the reported data that were obtained from the primary studies. The investigation of postoperative serum biomarkers with a longer follow-up period would be desirable in future studies. (5) A systemic increase in postoperative serum biomarkers such as CK, CRP, and Hb can be attributed to factors other than the THA approach. Such confounding factors might be infections or other inflammatory reactions, extensive postoperative rehabilitation, renal insufficiency, and adverse drug reactions.

5. Conclusions

Our meta-analysis indicates that there was no significant overall difference between MI THA and CA THA in terms of postoperative serum biomarkers (CK, CRP, and Hb). We found a slight advantage of MI THA in CRP values. MI THA had a 16 mg/L lower CRP value 3 days postoperatively than CA THA. MI THA had a 3 mg/L lower CRP value 4 days postoperatively than CA THA. However, these findings do not provide sufficient evidence to recommend changing the surgical approach from CA THA to MI THA, since the differences between the examined approaches did not seem to reach MCID.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/prosthesis5030049/s1, Table S1: PRISMA Checklist; Excel S2: Raw data extraction set.

Author Contributions: N.R.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing—original draft; P.M.-K.: Data curation, Formal analysis, Investigation, Methodology, Writing—review and editing; R.H.: Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Writing—review and editing; D.D.: Supervision, Writing—review and editing; R.B.: Supervision, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: Funded by the Brandenburg Medical School publication fund supported by the German Research Foundation and the Ministry of Science, Research and Cultural Affairs of the State of Brandenburg.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Raw data extraction set available in Excel S2.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ANFH avascular necrosis of the femoral head

BMI body mass index
CA conventional approach
CI confidence interval
CK creatine kinase

CNKI China National Knowledge Infrastructure

CRP C-reactive protein
Hb hemoglobin
HHS Harris Hip Score
ITT intention to treat

MCID minimal clinically important difference

MD mean difference
MI minimally invasive
PP per protocol analysis
RCT randomized controlled trials

SD standard deviation THA total hip arthroplasty

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