SYSTEMATIC REVIEW

The use of Three-Dimensional Printing in Orthopaedics: a Systematic Review and Meta-analysis

Olivia O'Connor, MD; Reece Patel, MD; Azeem Thahir, MD; Jamie SY. Ho, MD; Eric Jou, PhD

Research performed at School of Clinical Medicine, University Of Cambridge, Cambridge, United Kingdom

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Abstract

Objectives: 3D-printing is a rapidly developing technology with applications in orthopaedics including pre-operative planning, intraoperative guides, design of patient specific instruments and prosthetics, and education. Existing literature demonstrates that in the surgical treatment of a wide range of orthopaedic pathology, using 3D printing shows favourable outcomes. Despite this evidence 3D printing is not routinely used in orthopaedic practice. We aim to evaluate the advantages of 3D printing in orthopaedic surgery to demonstrate its widespread applications throughout the field.

Methods: We performed a comprehensive systematic review and meta-analysis. AMED, EMBASE, EMCARE, HMIC, PsycINFO, PubMed, BNI, CINAHL and Medline databases were searched using Healthcare Databases Advanced Search (HDAS) platform. The search was conducted to include papers published before 8th November 2020. Clinical trials, journal articles, Randomised Control Trials and Case Series were included across any area of orthopaedic surgery. The primary outcomes measured were operation time, blood loss, fluoroscopy time, bone fusion time and length of hospital stay.

Results: A total of 65 studies met the inclusion criteria and were reviewed, and 15 were suitable for the meta-analysis, producing a data set of 609 patients. The use of 3D printing in any of its recognised applications across orthopaedic surgery showed an overall reduction in operative time (SMD = -1.30; 95%CI: -1.73, -0.87), reduction in intraoperative blood loss (SMD = -1.58; 95%CI: -2.16, -1.00) and reduction in intraoperative fluoroscopy time (SMD = -1.86; 95%CI: -2.60, -1.12). There was no significant difference in length of hospital stay or in bone fusion time post-operatively.

Conclusion: The use of 3D printing in orthopaedics leads to an improvement in primary outcome measures showing reduced operative time, intraoperative blood loss and number of times fluoroscopy is used. With its wide-reaching applications and as the technology improves, 3D printing could become a valuable addition to an orthopaedic surgeon's toolbox.

Level of evidence: I

Keywords: Orthopedic, Printing, Review, Systematic, Three dimensional

Introduction

Three-dimensional (3D) printing refers to a manufacturing technology that is used to create a three-dimensional object from a digitally designed model. Although its uses in medicine are relatively new, it is not a new technology. 3D printing technology was first developed as "stereolithography" in the early 1980's, with commercial printers becoming available later that decade. [1] However, since then 3D printing has revolutionised the design and manufacturing processes in many different industries, allowing faster production, increased customisation, and rapid refinement. As the technology developed, 3D printing has become more accessible, more applicable and more cost effective [2]; thus, facilitating it to emergence into the medical field.

The uses of 3D printing in orthopaedic surgery can be split in six main categories: (1) Surgical planning, (2) Surgical implants, (3) Surgical instruments, (4) Surgical training, (5) Fracture fixations devices and (6) Orthotics; the most

Corresponding Author: Olivia O'Connor, Department of Trauma and Orthopaedics, Addenbrookes Major Trauma Unit, Cambridge/ School of Clinical Medicine, University Of Cambridge, Cambridge, United Kingdom University Hospitals, United Kingdom

Email: olivia.oconnor1@ouh.nhs.uk

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common of these being its use in surgical planning, surgical implants and surgical instruments. In surgical planning, 3D printing allows surgeons to print a 3D model to visualise the anatomy and better prepare for complex operations. For example, 3D models were created to guide incision, placement of clamps, and the placement of plates and screws in the reduction of complex acetabular fractures. [3] 3D printed surgical implants are often seen as more customisable, and allow for patient-specific needs to be met, for example in complex foot and ankle pathologies. [4] Surgical instruments, such as surgical tools and guides can be used to aid operations, allowing for more accurate deformity correction or resection, implant placement and reducing operative time. [5]

There have been a number of primary studies published on the applications of 3D printing in orthopaedics, especially over the last few years. There have also been some literature reviews giving an overview of 3D printing in orthopaedics and showing possible future directions. [6,7] There has been a recent systematic review and meta-analysis on the use of 3D printing in pre-operative planning in orthopaedic surgery, which found 3D printing reduces operative time, intraoperative blood loss and the number of times fluoroscopy is used. [8] However, to our knowledge, there are no recent systematic review and meta-analyses on the clinical applications and surgical outcomes of 3D printing as a whole in orthopaedic surgery. Therefore, the aim of this systematic review and meta-analysis was to analyse studies from all areas of orthopaedic surgery to determine the clinical applications and assess surgical outcomes. We wanted to determine if the use of 3D printing in orthopaedic surgery reduced operative time, blood loss, and fluoroscopy time. We also analysed bone fusion time, and length of hospital stay.

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used throughout this systematic review. [9]

To identify all the relevant studies relating to 3D printing in orthopaedic surgery a thorough search was conducted. AMED, EMBASE, EMCARE, HMIC, PsycINFO, PubMed, BNI, CINAHL and Medline databases were searched using Healthcare Databases Advanced Search (HDAS) platform. The search was conducted to include papers published before 8th November 2020.

In order to capture articles on 3D printing the following keywords were searched: '3D Printing', '3-dimensional printing', 'three-dimensional printing', 'additive manufacturing', 'rapid manufacturing', 'stereolithography', 'Selective Laser Sintering', 'fused deposition modelling', 'printed scaffold', 'inkjet printing', '3D modelling', '3-dimensional modelling' 'three-dimensional modelling', 'computed aided design', 'computed aided modelling', 'Additive printing', and 'reverse engineering'. These terms were used in combination with the orthopaedic keywords 'Ortho', 'orthopaedics', 'bone' and 'joint'. The search also excluded the keywords 'jaw', 'maxillofacial', 'craniofacial', 'orthognathic', 'mandibular', 'dental', 'neurosurgery', 'skull', 'ribs', 'cardiothoracic', 'bioprinting', '3D navigation', '3D planning' to remove articles on cranial, maxillofacial and cardiothoracic surgery as well as articles that use techniques other than 3D printing.

After duplicates were removed, three independent researchers conducted an abstract screen and excluded animal studies, simulator studies, experimental studies and cadaver studies. This was to ensure all studies included were applicable to the use of orthopaedic surgery on humans in today's practice. Only papers with full text available in English were considered, as we did not have the ability for accurate translation for papers written in languages other than English. Clinical trials, journal articles, Randomised Control Trials and Case Series were included across any area of orthopaedic surgery. After this screening process, 65 papers were found to be relevant and were included in this review. Two independent researchers extracted the following data from these papers: Year of publication, Country of origin, Study design, Number of patients, 3D-printing materials and technique, Cost, Patient opinion, Surgical opinion, and Surgical outcomes (Operation time, blood loss, fluoroscopy time, healing time, length of hospital stay). A PRISMA flow diagram of the search strategy is provided in [Figure 1].

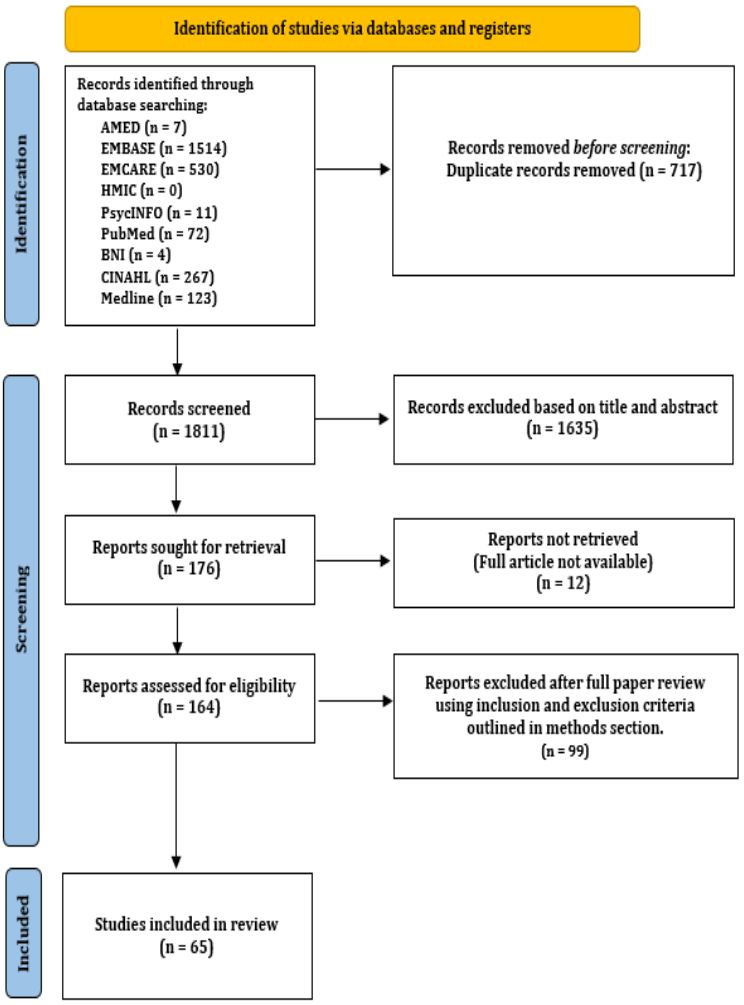

Figure 1. Figure 1: PRISM Flow diagram summarising study selection process.

We used the population, intervention, comparison, outcome (PICO) framework to develop our search strategy and main questions for the meta-analysis. We analysed the use of 3D printing in all aspects of orthopaedic surgery to ascertain whether it's use reduced operative time, blood loss fluoroscopy time, bone fusion time, and length of hospital stay compared to when 3D printing was not used.

Quality assessment

The GRADE criteria [10] was used to perform the quality assessment on the included papers [Supplementary Table 1]. For the clinical studies, the risk of bias assessments were conducted using the RoB2 tool [11] for randomised control trials [Supplementary Table 2], and the ROBINS-I tool [12] for non-randomised control trials [Supplementary Table 3]. After a thorough search, no risk of bias assessment tool could be found to assess the non-animal preclinical studies included in our review. Therefore, in order to assess the risk of bias of the pre-clinical studies we created our own risk of bias tool. This was done by selecting the relevant risk of bias domains from a list of regularly used domains reported by Wang et al. [13] The risk of bias domains we selected are shown in [Supplementary Table 4]. The supplementary tables include the risk of bias analyses, which includes a number of bias domains including publication bias.

Statistical analysis

Statistical analysis was conducted using Review Manager (RevMan Computer program, Version 5.4.1, The Cochrane Collaboration, 2020). A primary meta-analysis was performed using the DerSimonian-Laird random-effects model to calculate the pooled estimate of the standardised mean differences (SMD) in operative time, blood loss, fluoroscopy time, duration for bone fusion and length of hospital stay between the 3D printing and conventional management groups. A negative SMD suggested that 3D printing was superior to conventional surgery, and forest plots were generated with 95% confidence intervals (95% CIs). The I2 value was used to estimate heterogeneity, with the thresholds of 0-40% as no important heterogeneity, 30-60% as moderate, 50-90% as substantial and 75-100% as considerable heterogeneity. [14]

Results

Characteristics of included studies

After exclusion criteria were applied 65 papers were found to be relevant. Of the 65 studies, 11 were randomised control trials (RCTs), ten were case series, 16 were retrospective case series, 15 were pre-clinical trials, two were retrospective studies, ten were cohort studies and one was a cross-sectional observational study.

The included studies were conducted in 17 different countries, and the five most represented countries were China (n=27, 41.5%), USA (n=10, 15.4%), UK (n=5, 7.7%), South Korea (n=4, 6.2%), and Italy (n=4, 6.2%).

There were eight applications of 3D printing reported including model for surgical planning (n=17, 26.2%), surgical implants (n=13, 20.0%), surgical guides (n=13, 20.0%), surgical training (n=5, 7.7%), conservative fracture fixations (n=4, 6.2%), surgical tools (n=2, 3.1%), orthotics (n=1, 1.5%), and external fixation (n=1, 1.5%).

The 3D printing techniques used were also extracted with 12 different 3D printing techniques being used. The five most commonly used techniques were fused deposition modelling (n=13, 20.0%), selective laser sintering (n=11, 16.9%), stereolithography (n=8, 12.3%), inkjet like 3D printing (n=7, 10.8%), and electron beam melting (n=4, 6.2%). Six studies used multiple 3D printing techniques.

We extracted five different surgical outcomes from the studies: 15 studies investigated operative time, 11 investigated blood loss, seven investigated blood loss, four measured time taken for bone fusion and two calculated length of hospital stay.

Meta-analysis

Studies with comparison groups and reporting surgical outcomes were included in the meta-analysis. Of the 65 studies that were found to be relevant, 15 studies were suitable for the meta-analysis, producing a data set of 609 patients. The characteristics of the studies included in the meta-analysis are shown in [Table 1].

Table 1. Characteristics of studies included in the meta-analysis

Author	Country	Year	Study type	n 3D	n control	M/F	Age, y (SD)	Orthopaedic condition	Use of 3D printing	FU duration (SD)
Cai et al.	China	2020	Cohort study	15	28	30/13	38.0 (range 18-56)	AVN of femoral head	Surgical planning	14 months
Duan et al.	China	2019	Cohort study	14	16	NR	52.0 (19.0)	Subtalar joint arthrodesis	Surgical guide	1.8 (0.7) years
Giannetti et al.	Italy	2016	Cohort study	16	24	22/18	43.2 (range 23-65)	Displaced tibial plateau fracture	Surgical planning	13.3 (range 11-21) months
Tian et al.	China	2018	Cohort study	31	31	9/53	67.6 (7.9)	Total knee arthroplasty	Surgical instrument	38 (31-47) months
Wang et al.	China	2018	Cohort study	21	25	14/32	71.0 (5.8)	Proximal third humeral shaft fracture	Surgical guide	16.9 (5.1) months
Wang X et al.	China	2019	Cohort study	8	12	8/12	26.0 (8.0)	Periacetabular osteotomy	Surgical guide	13 (5) months

Table 1. Continued

Chen et al.	China	2019	RCT	23	25	31/15	38.7 (13.6)	AO type C distal radius fractures	Surgical planning	13.1 (0.7) months
Huang et al.	China	2020	RCT	20	20	26/14	43.4 (11.6)	Both-column acetabular fractures	Surgical planning	NR
Kong et al.	China	2020	RCT	16	16	19/13	42.0 (5.9)	Intra-articular distal radial fracture	Surgical planning	6 months
Liu K et al.	China	2020	RCT	18	38	28/28	17.5 (range 12-19.5)	Pelvic osteotomy	Surgical planning	24 months
Ozturk et al.	Turkey	2020	RCT	10	10	18/2	43.0 (18.7)	High-energy tibial plateau fracture	Surgical planning	9.8 (3.3) months
Wang Xiji et al.	Japan	2019	RCT	10	10	8/12	57.7 (7.0)	Lumbar cortical bone trajectory screw fixation	Surgical guide	NR
Wan L et al.	China	2019	RCT	48	48	66/30	43.4 (4.5)	Complex acetabular fracture	Surgical planning	NR
Yang et al.	China	2017	RCT	20	20	28/12	38.6 (range 23-61)	Elbow fracture	Surgical planning	NR
Yin et al.	China	2020	RCT	8	8	15/1	28.0 (6.9)	Scaphoid nonunion	Surgical planning	6 months

Operative time

All 15 studies investigated operative time, of which nine were RCTs. [15–23] Meta-analysis revealed a statistically significant reduction in operative time (Standardised Mean Difference (SMD) = -1.30; 95%CI: -1.73, -0.87) in the 3D printing groups compared to the control groups [Figure 2.1]. There was substantial heterogeneity in the data (I^2 = 81%).

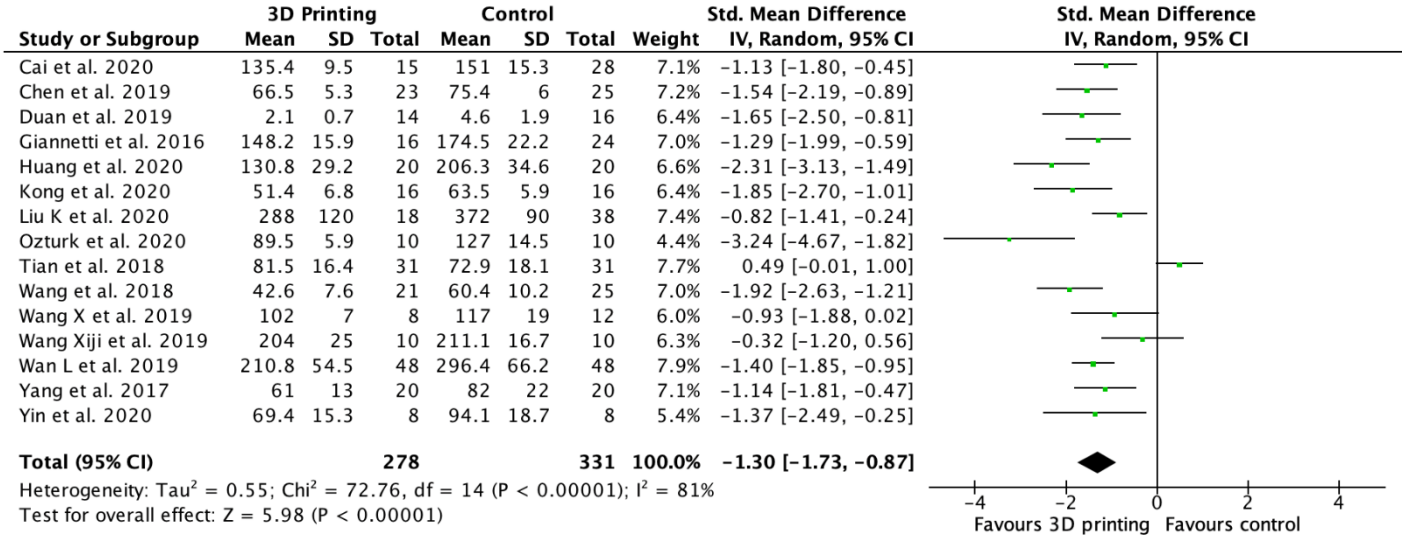

Figure 2.1. Forest plot of comparison: 3D printing versus conventional surgery, outcome: Operative time (min)

Intra-operative blood loss

Blood loss was measured in 11 of the 15 studies, seven of which were RCTs. [3,15–17,19,20,22] This created a data set of 467 patients. Meta-analysis showed that there was a statistically significant reduction in blood loss (SMD = -1.58; 95%CI: -2.16, -1.00) in the 3D printing groups compared to the control groups [Figure 2.2]. There was a substantially high heterogeneity in this data (I^2 = 84%).

Fluoroscopy time

Fluoroscopy time was measured in seven studies creating a data set of 286 patients. Five of these studies were RCTs. [3,15–17,19] Meta-analysis of this data showed there was a statistically significant reduction in fluoroscopy time (SMD = -1.86; 95%CI: -2.60, -1.12) in the 3D printing groups compared to the control groups [Figure 2.3]. The heterogeneity of this data was I^2 = 83%.

Bone fusion

Time taken for bone fusion was measured in four studies with a total data set of 136 patients. Two of these studies were RCTs. [16,19] Meta-analysis revealed a difference in time

taken for bone fusion (SMD = -0.30; 95%CI: -0.84, 0.25) in the 3D printing groups compared to the control groups [Figure 2.4]. The 95% confidence interval overlapping with 0 indicates these results are not statistically significant at 5% significance levels. The heterogeneity of this data was substantial with I^2 = 58%.

Length of hospital stay

Length of hospital stay was measured in two studies both of which are RCTs. [18,20] This created a data set of 76 patients. Pooled estimation revealed a difference in length of hospital stay (SMD = -0.58; 95%CI: -1.16, 0.01) in the 3D printing groups compared to the control groups [Figure 2.5]. The 95% confidence interval overlapping with 0 indicates these results are not statistically significant at 5% significance levels. There was an insignificant heterogeneity in this data (I^2 = 26%).

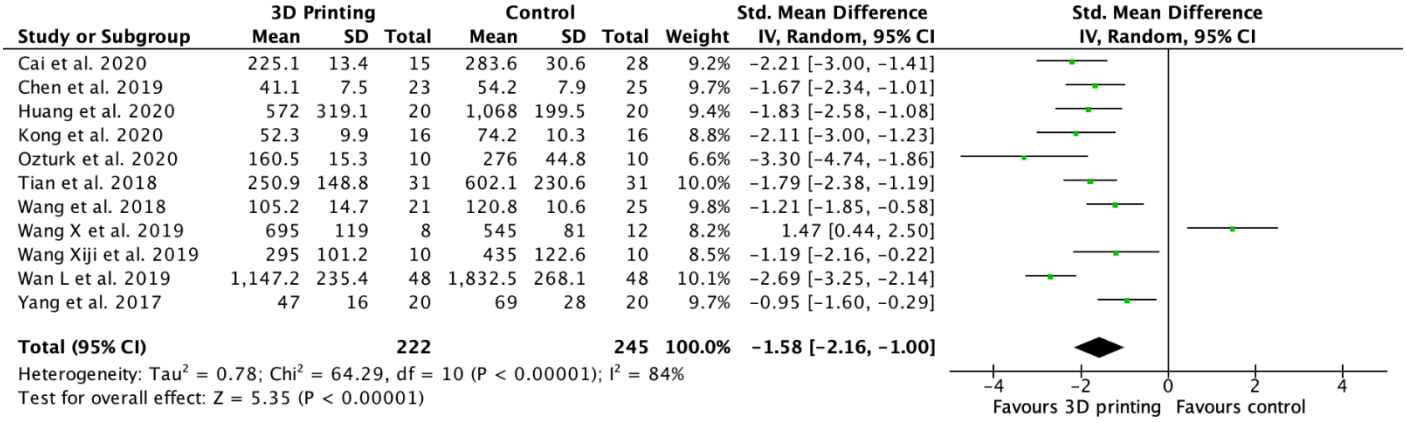

Figure 2.2. Forest plot of comparison: 3D printing versus conventional, outcome: Blood loss (ml)

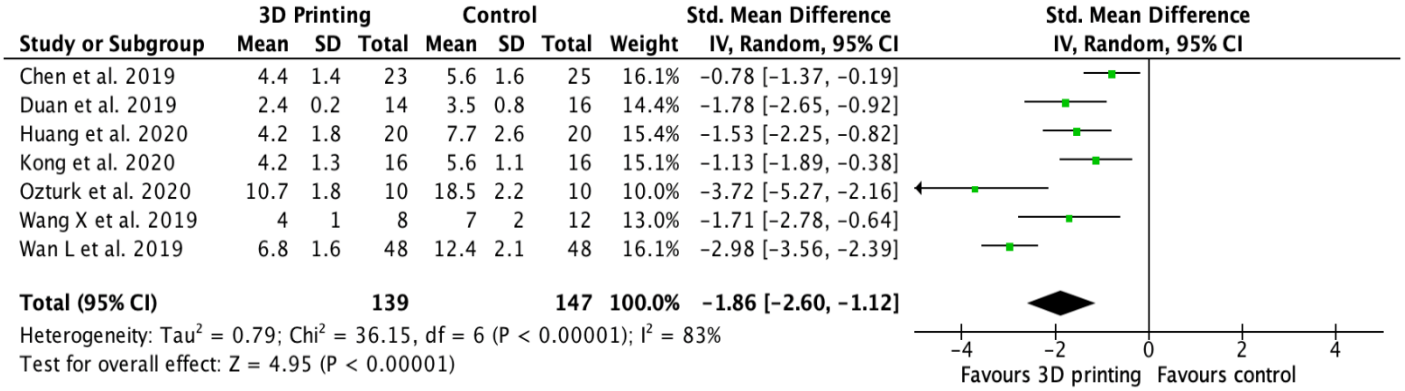

Figure 2.3. Forest plot of comparison: 3D printing versus conventional, outcome: Fluoroscopy time (min)

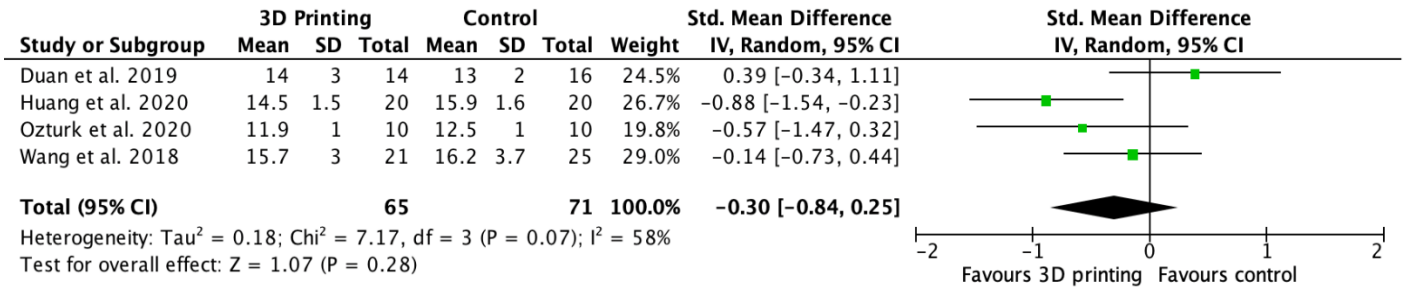

Figure 2.4. Forest plot of comparison: 3D printing versus conventional, outcome: Bone fusion (weeks)

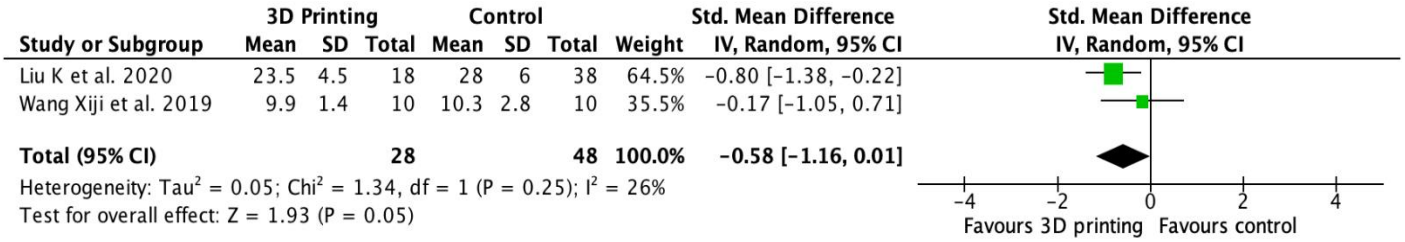

Figure 2.5. Forest plot of comparison: 3D printing versus conventional, outcome: Length of hospital stay (days)

Subgroup analyses are also performed separating RCT and cohort studies, which showed that in each of the two individual groups, 3D printing is associated with reduced operation time and volume of blood loss [Figure 3]. Importantly, there was no significant differences in operative time and blood loss between the RCTs and cohort studies, indicating that the findings from the two different types of studies show a high degree of concordance.

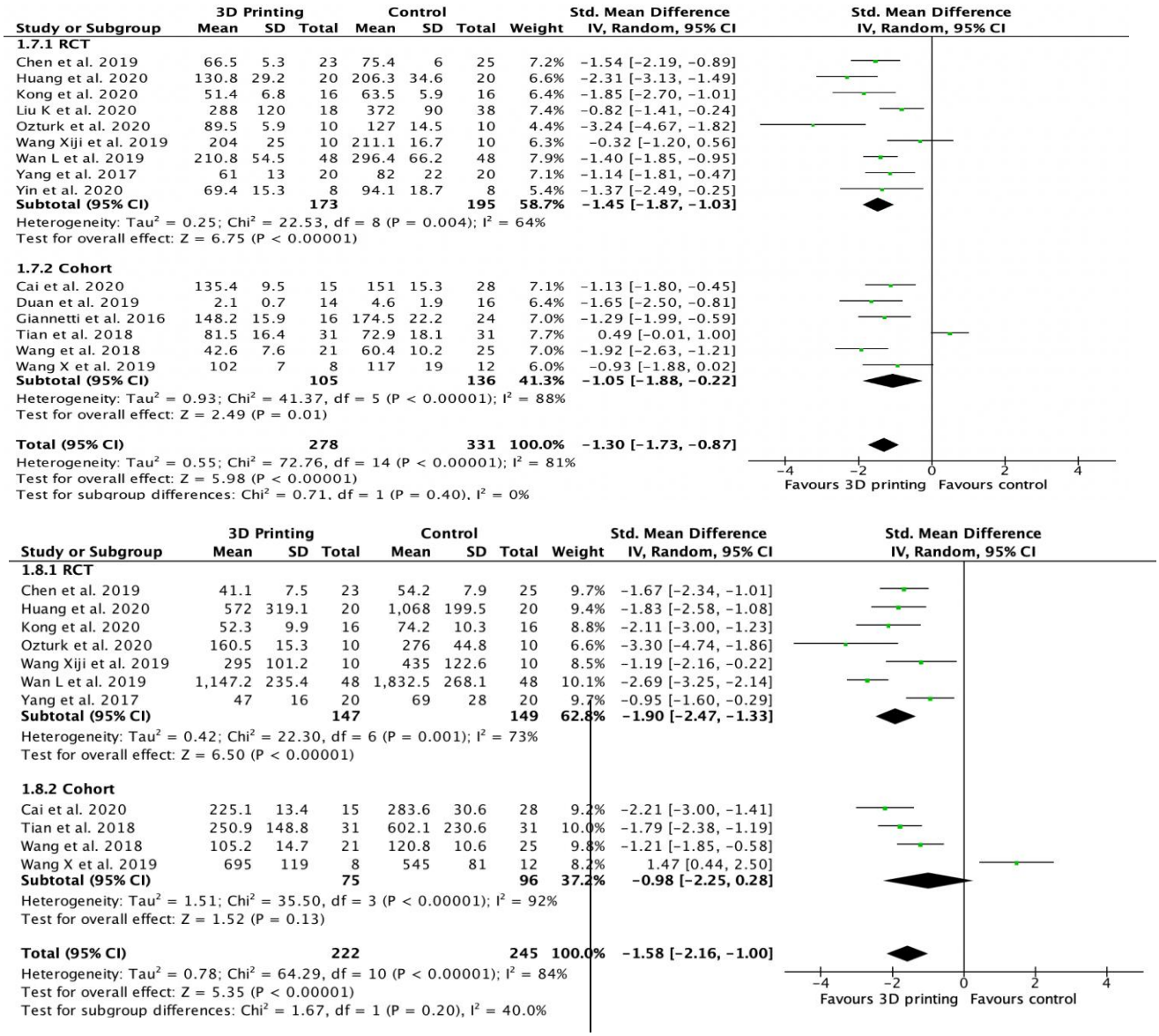

Figure 3. Subgroup analysis of RCTs-only and cohort studies-only for the outcomes (a) operative time and (b) blood loss

Discussion

From our results and meta-analysis we have found that the use of 3D printing in orthopaedics leads to a statistically significant reduction in operative time, intraoperative blood loss, and fluoroscopy time. This has been shown in a variety of different operation types [Table 1], including fracture fixation, osteotomy and arthroplasty. There was also a non-statistically significant reduction in both bone fusion time and length of hospital stay.

In all but one paper included in the meta-analysis, use of 3D printing was shown to reduce operative time. Reasons hypothesized for this reduction in operative time differed depending on the specific application of 3D printing utilized. For example, in those papers which used 3D printing to produce a model of the fractured bone for preoperative selection of appropriate plates and screws for fixation, operative time was reduced as fewer adjustments to selected plates and screws had to be made intraoperatively as compared to the control groups. [3,15–17,19,24,25] In those papers which used 3D printing to produce a surgical guide or templates for aspects of the surgical procedure for example insertion of K-wires or as a template for bone cutting, operative time was reduced due to reduction of surgical uncertainty and fewer revisions needed intraoperatively. [20,23,26–28] The only paper which reported an increase in operative time was that by Tian et al, in which patient specific instruments (PSIs) were generated using 3D printing. [29] It was hypothesised that there is a learning curve with using PSIs, and once the surgeon surpasses the learning curve operative time will reduce. Applying this argument to the other papers, it is remarkable that operative time was shown to be reduced when 3D printing is such a novel technology and the application to surgical procedure will therefore require a learning curve. Indeed, a recent RCT published after the search date of the present meta-analysis similarly revealed a significant reduction in operation time in patients treated for displaced and intra-articular calcaneal fractures upon incorporation of 3D printing during the perioperative stage.[30] The reduction in operative time has been shown to be clinically relevant as a meta-analysis has demonstrated a 14% increase in complications for every 30 minutes of additional operating time.[31] Therefore, the reduction in operative time that 3D printing may bring, could directly reduce complication rate, and benefit patient care.

It may be argued that despite the reductions in operative time shown in the meta-analysis, the overall time spent to treat each patient is increased when factoring in the time for manufacturing of the models. However, reducing intraoperative time in orthopaedic surgery has been shown to reduce the risk of short-term complications such as surgical site infections, reoperation and mortality. [32–34] Additionally, longer operative times lead to markedly increased costs- in 2016, NHS orthopaedic theatres cost £24.77 per minute to run. [35] The paper by Yin et al estimated a cost of $300 (£219 on 31/12/2020) per 3D printed surgical guide, so in this example paper, use of 3D printing for surgical guides in scaphoid non-union fractures would have been cost effective with the £219 to produce the model being overshadowed by the reduction of an estimated £625 due to the resulting decrease in the operative time associated with the use of the 3D printed model (but note this estimate does not factor in additional medical costs for example, the costs of CT scans used to create the models). [23] Additionally, it has been hypothesised that as the technology further advances the cost of 3D printing will further reduce further exacerbating the economic benefits.

Intraoperative blood loss was reduced in all but one of the papers included in our meta-analysis. This could be attributed to the shorter operative times. Wang et al reported an non-significant increase in intraoperative blood loss attributing this outlying result to unskilled installation of the cutting template for use in bernese periacetabular osteotomy for developmental dysplasia of the hip. [28] This led to an increased dissection scope of the soft tissue particularly in the first few cases. They noticed blood loss decreased as the technique of the surgeons improved with more experience installing the template. As techniques become more refined, blood loss intraoperatively will decrease even further.

Intraoperative fluoroscopy time was reduced in all papers included in our meta-analysis which assessed fluoroscopy time, which is beneficial both in terms of reduced costs and reduced radiation exposure. However, for all the papers which studied fluoroscopy time, CT scans were used to aid the design of the 3D printed component. There is little literature which compares the amount of radiation using CT to intraoperative fluoroscopy. It has been shown that the use of fluoroscopy reduces the dose of radiation delivered to both patients and staff when compared with a standard CT scan. [36] Increased use of CT scanning in preoperative planning may therefore nullify the benefits reaped in terms of reduced radiation exposure for the patient due to reductions in fluoroscopy time. However, reduced intra-operative fluoroscopy time would reduce radiation exposure to the operating surgeons and theatre staff.

This systematic review looked at 3D printing in orthopaedics taking a broader view than much of the existing literature. However, when comparing our results to other systematic reviews already published in the field of 3D printing in orthopaedics with more focused applications, we saw comparable trends. Morgan et al showed when exclusively applied to preoperative planning in orthopaedic trauma, the use of 3D printing reduced intraoperative time, blood loss and intraoperative fluoroscopy. [8] The use of 3D printing in the treatment of individual orthopaedic pathologies has been the subject of a number of systematic reviews showing reduced intraoperative time and blood loss in the context of the treatment of complex pelvic and acetabular fractures [37,38] proximal humerus fractures [39] and displaced intra-articular calcaneal fractures. [40] Despite the support in the literature for its use, there are no existing guidelines in the UK from either National Institute of Clinical Excellence or British Orthopaedics Association which recommend the use of 3D printing in the routine treatment of orthopaedic pathology. With the improving costs of 3D printing and literature supporting its application, such as in pre-operative planning, it is possible we will see 3D printing

incorporated into clinical guidelines in the near future.

Limitation

Limitations of this meta-analysis lie in the sample sizes used in each of the papers included. A total of 278 patients treated using 3D printing were included in this meta-analysis with some of the included studies drawing results from as few as eight patients. Additionally, the broad scope of the paper means that it is difficult to draw conclusions about separate applications of 3D printing (for example preoperative planning, prosthesis design, implant design). This information would be useful in furthering the application of orthopaedics in routine clinical practice, as recommendations for its use to governing clinical bodies will ultimately be made based on data available for each of these separate applications, not data available regarding the use of 3D printing as a whole. Furthermore, the systematic review and meta-analysis search was performed on November 2020, and therefore studies published after this date are not incorporated in the meta-analysis. Importantly, studies published after the search date, for example by Lu and colleagues, showed highly concordant results to the present systematic review.[30] In that RCT of patients with displaced and intra-articular calcaneal fractures, use of perioperative 3D printing led to a reduction in operation duration, volume of blood loss and number of fluoroscopy used compared to the control group whom received conventional surgery. These findings are highly concordant to the present meta-analysis which similarly found 3D printing for orthopaedic procedures to be associated with shorter operative time, less blood loss and reduced intraoperative fluoroscopy time. Together, the high consistency between the present meta-analysis and studies published after the search date complement each other and strengthens the overall findings that 3D printing has significant benefits in orthopaedic surgery. Finally this meta-analysis did not look at clinical outcomes for patients despite data being available for many of the papers included. Since the papers included each focused on different orthopaedic pathologies, different clinical outcome scores were employed for different surgeries for instance the Knee Society score or the Harris Hip score so creating homogenous data for this paper with a broad scope using multiple different indices would prove difficult. In four of the papers, secondary outcome measures were significantly improved with the use of 3D printing.[16,18,27,28] Nine papers showed no difference in clinical outcomes, and two did not comment. Data on secondary outcome measures including postoperative function and pain scores are likely to prove vital in informing recommendations in future guidelines, given the weight placed on post-operative quality of life for patients in orthopaedics.

A limitation of this meta-analysis when looking specifically at operative time is that each of the papers had a different definition of operative time, for instance Duan et al defined operative time as the time to drill the K-wires, whilst Liu eat al., 2020 defined it as time from skin opening to skin closure.[18,26] This means that reduction in operative time with 3D printing will appear relatively greater in those papers which define operative time as only the aspect of the operation on which 3D printing will have an impact, for example those which define operative time as time to drill K-wires. In order to have a more accurate estimate of the impact of 3D printing on operating time a consistent definition of operative time would be useful.

Conclusion

The use of 3D printing in orthopaedics is rapidly progressing with the development of the technology. This review has shown the use of 3D printing in orthopaedics generally yields significant improvements in the primary outcomes of operative time, blood loss and intraoperative fluoroscopy use. As the use of 3D printing becomes cheaper and more accessible, further work should be carried out to assess secondary outcome measures to allow the technology's incorporation into routine clinical practice and clinical guidelines.

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Olivia O'Connor MD [1,2]*
Reece Patel MD [1,2]*
Azeem Thahir MD [1]
Jamie SY. Ho MD [3]
Eric Jou PhD [4,5]

1 Department of Trauma and Orthopaedics, Addenbrookes Major Trauma Unit, Cambridge University Hospitals, United Kingdom

2 School of Clinical Medicine, University Of Cambridge, Cambridge, United Kingdom

3 Department of Medicine, Royal Free London NHS Foundation Trust, London, United Kingdom

4 Kellogg College, University of Oxford, Oxford, United Kingdom

5 Medical Sciences Division, Oxford University Hospitals, University of Oxford, Oxford, United Kingdom

* Contributed equally to this article as first authors

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Supplementary table 1. GRADE criteria for quality assessment of the included papers

Author	Study Design	Risk of Bias	Imprecision	Inconsistency	Indirectness	Publication Bias	Large Effect	Plausible confounding	Quality
Ozturk A.M.; Suer O.; Aktuglu K.; Derin O.; Ozer M.A.; Govsa F.	Randomised control trial	High	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Maier J.; Weiherer M.; Palm C.; Huber M.	Pre-clinical trial	Low	Not serious	Not serious	Not serious	Not serious	No	No	High
Yin H.-W.; Feng J.-T.; Yu B.-F.; Shen Y.-D.; Gu Y.-D.; Xu W.-D.	Randomised control trial	Low	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Lipskas J.; Yao W.; Deep K.	Pre-clinical trial	Low	Not serious	Not serious	Serious	Not serious	N/A	No	High
Hasan S.; Hamersveld K.T.V.; Mheen P.J.M.-V.; Kaptein B.L.; Nelissen R.G.H.H.; Toksvig-Larsen S.	Randomised control trial	Low	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Wang K.C.; Leong N.; Hasan S.A.; Siegel E.L.; Jones A.; Kambhampati S.; Shiu B.; Liacouras P.C.; Stuelke S.	Retrospective study	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
Wang X.; Zhu Z.; Peng J.; Chen X. (chenxdmd@163.com); Liu S.; Zhang L.; Guan J.	Cohort study	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Jovicic M.S.; Ribicic T.; Simunic S.; Vuletic F.; Petrovic T.; Kolundzic R. (robert.kolundzic@zg.t-com.hr)	Retrospective case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Chen J.V.; Dang A.B.C.; Lee C.S.	Pre-clinical trial	Moderate	Not serious	Not serious	Not serious	Serious	N/A	No	Moderate
Punyaratabandhu T.; Pairojboriboon S.; Liacouras P.C.	Case series	High	Serious	Not serious	Not serious	Not serious	N/A	No	Moderate
Hao J.; Wu Y.Y.; Rajaraman M.; Shimada K.; Nangunoori R.; Cook D.; Yu A.; Cheng B.	Pre-clinical trial	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	Yes	High
Wang X.J.; Sun H.H.; Zhang Y.Y.; Yang R.Z.; Hao D.J.	Cohort study	Low	Not serious	Not serious	Not serious	Serious	N/A	No	Moderate

Supplementary table 1. Continued

Chaoyan H.; Zhifang W.; Fei H.; Runai Y.; Peiyi X.; Yiwen L.; Yanjun C.	Randomised control trial	High	Not serious	Not serious	Not serious	Not serious	N/A	No	Moderate
Wei F.; Li Z.; Liu Z.; Liu X.; Jiang L.; Yu M.; Xu N.; Wu F.; Dang L.; Zhou H.; Cai H.	Retrospective case series	Low	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
Angelini A.; Trovarelli G.; Ruggieri P.; Kotrych D.; Bohatyrewicz A.; Szafranski A.	Retrospective case series	Moderate	Not serious	Not serious	Some concerns	Not serious	N/A	Yes	Moderate
Farrell D.A.; Miller T.J.; Chambers J.R.; Joseph V.A.; McClellan W.T.	Pre-clinical trial	High	Serious	Not serious	Serious	Not serious	N/A	No	Low
Samaila E.M.; Negri S.; Maluta T.; Magnan B.; Zardini A.; Rossignoli C.; Bizzotto N.	Cohort study	Moderate	Not serious	Not serious	Some concerns	Not serious	N/A	No	High
Horas K.; Hoffmann R.; Faulenbach M.; Heinz S.M.; Schweigkofler U.; Langheinrich A.	Case series	High	Serious	Not serious	Some concerns	Not serious	N/A	No	Low
Cai X.; Xu Y.; Yu K.; He X.; Luo H.; Duan J.; Wu Y.	Cohort study	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Park J.W.; Kang H.G. (ostumor@ncc.re.kr); Kim J.H.; Kim H.-S.	Retrospective case series	Moderate	Serious	Not serious	Not serious	Not serious	N/A	Yes	Moderate
Huang J.-H.; Liao H.; Tan X.-Y.; Zhou Q.; Cao H.-Y.; Zeng C.-J.; Zheng Y.-S.; Xing W.-R.	Prospective case control study	Low	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Liu W.; Shao Z.; Hu B.; Wu Q.; Hu H.; Zhang S.; Wang B.; Rai S.	Retrospective case series	Moderate	Not serious	Not serious	Some concerns	Some concerns	N/A	Yes	Moderate
Stefan P.; Pfandler M.; Lazarovici M.; Weigl M.; Navab N.; Euler E.; Furmetz J.; Weidert S.	Pre-clinical trial	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Liu K.; Li Z.; Ma Y.; Lian H.	Randomised control trial	Low	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Hu H.; Liu W.; Wang S.; Zhang Z.; Liu J.; Shao Z. (szwpro@163.com); Wang B. (wangbaichuan-112@163.com); Zeng Q.; Zhang Y.	Retrospective case series	Moderate	Serious	Not serious	Serious	Not serious	N/A	Yes	Low
Tilton M.; Manogharan G.P.; Armstrong A.; Lewis G.S.; Sanville J.; Chin M.; Hast M.W.	Pre-clinical trial	Low	Not serious	Not serious	Some concerns	Some concerns	N/A	No	High
Blaya F.; Pedro P.S.; Lopez-Silva J.; D'Amato R.; Pedro A.B.S.; Juanes J.A.	Pre-clinical trial	Low	Not serious	Not serious	Serious	Not serious	N/A	No	Moderate
Javan R.; Ellenbogen A.L.; Haji-Momenian S.; Greek N.	Pre-clinical trial	High	Serious	Not serious	Serious	Some concerns	N/A	No	Low
Mishra A.; Verma T.; Vaish A.; Vaish R.; Maini L.; Vaishya R.	Case series	High	Serious	Not serious	Some concerns	Not serious	N/A	No	Low
Duan X.-J.; Fan H.-Q.; Wang F.-Y.; Yang L.; He P.	Cohort study	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
van Duren B.H.; Pandit H.; Lebe M.; Davies D.C.; Somashekar N.	Pre-clinical trial	High	Serious	Not serious	Some concerns	Some concerns	N/A	No	Low
Wan L.; Zhang X.; Zhang S.; Li K.; Cao P.; Li J.; Wu G.	Randomised control trial	High	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Wan J.; Zhang C.; Liu Y.-P.; He H.-B.	Retrospective case series	Moderate	Not serious	Not serious	Some concerns	Not serious	N/A	No	Moderate
Xu J.; Zhong S.; Huang W.; He Z.; Wei C.; Zheng Y.; Li W.; Zhang G.; Lin H.; Chen Y.	Cohort study	High	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Tracey J.; Arora D.; Gross C.E.; Parekh S.G.	Retrospective case series	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate

Supplementary table 1. Continued

Tomazevic M.; Kristan A.; Cimerman M.; Kamath A.F.	Pre-clinical trial	Moderate	Not serious	Not serious	Some concerns	Not serious	N/A	No	Moderate
Dekker T.J.; Steele J.R.; Federer A.E.; Hamid K.S.; Adams S.B.	Retrospective case series	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	Moderate
Girolami M.; Bandiera S.; Barbanti-Brodano G.; Ghermandi R.; Terzi S.; Tedesco G.; Evangelisti G.; Pipola V.; Gasbarrini A.; Boriani S.	Retrospective case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Park J.W.; Kang H.G.; Kim J.H.; Park D.W.; Lim K.M.; Kim H.S.	Retrospective case series	High	Not serious	Not serious	Some concerns	Not serious	N/A	No	Moderate
Gorbatov R.O.; Malyshev E.E.; Romanov A.D.; Karyakin N.N.	Retrospective case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Tian H.; Zhao M.-W.; Geng X.; Zhou Q.-Y.; Li Y.	Cohort study	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Liu Y.; Zhou W.; Xia T.; Liu J.; Mi B.-B.; Hu L.-C.; Shao Z.-W.; Liu G.-H.	Cohort study	Moderate	Not serious	Not serious	Serious	Some concerns	N/A	No	Low
Wang Q.; Guan J.; Chen Y.; Wang L.; Hu J.	Cohort study	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Bauer A.S.; Storelli D.A.R.; Mccarroll H.R.; Lattanza L.L.; Sibbel S.E.	Retrospective case series	High	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
Zang C.-W.; Zhang J.-L.; Meng Z.-Z.; Liu L.-F.; Zhang W.-Z.; Chen Y.-X.; Cong R.	Case series	Moderate	Not serious	Not serious	Serious	Not serious	N/A	No	Moderate
Giannetti S.; Stancati A.; Santucci A.; Bizzotto N.	Cohort study	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Liang H.; Ji T.; Zhang Y.; Wang Y.; Guo W.	Retrospective case series	High	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
Ma L.; Zhou Y.; Lin Z.; Chen L.; Xia H.; Zhu Y.; Mao C.; Zhang Y.	Case series	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Luo W.; Huang L.; Liu H.; Qu W.; Zhao X.; Wang C.; Li C.; Yu T.; Han Q.; Wang J. (jinchengwang2015@gmail.com); Qin Y. (yanguoqin2015@gmail.com)	Case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Cazon A.; Kelly S.; Paterson A.M.; Bibb R.J.; Campbell R.I.	Pre-clinical trial	Moderate	Serious	Not serious	Some concerns	Not serious	N/A	No	Moderate
Allan R.; Woodburn J.; Abbott M.; Steultjens M.P.; Telfer S.	Cross-sectional observational study	Low	Not serious	Not serious	Some concerns	Not serious	N/A	No	High
Li H.; Qu X.; Mao Y.; Dai K.; Zhu Z. (zhenan_zhu@126.com)	Retrospective case series	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Burzynska K.; Filipiak J.; Morasiewicz P.	Pre-clinical trial	High	Not serious	Not serious	Serious	Some concerns	N/A	No	Low
Serra T.; Capelli C.; Toumpaniari R.; Orriss I.R.; Leong J.J.; Dalgarno K.; Kalaskar D.M.	Pre-clinical trial	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	High
Ma L.; Wang Y.; Zhou Y.; Zhu Y.; Mao C.; Lin Z.; Zhang Y.; Xia H.	Case series	Moderate	Not serious	Not serious	Serious	Not serious	N/A	No	Moderate
Storelli D.A.; Bauer A.S.; Lattanza L.L.; McCarroll H.R.	Case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Ozturk A.M.; Suer O.; Coban I.; Ozer M.A.; Govsa F.	Case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low
Nam H.-S.; Kim D.H.; Park D.-S.; Seo C.H.; Joo S.-Y.	Case series	High	Not serious	Not serious	Serious	Not serious	N/A	Yes	Low

Supplementary table 1. Continued

Ozturk; Suer, Onur; Derin, Okan; Ozer, Mehmet Asim; Govsa, Figen; Aktuglu, Kemal	Randomised control trial	High	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Gang Yang; Jian Yu; Yanqing Zhou; Sujuan Li; Quanhui Zheng; Bing Zhang; Kong, Lingde; Yang, Gang; Yu, Jian; Zhou, Yanqing; Li, Sujuan; Zheng, Quanhui; Zhang, Bing	Randomised control trial	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Kang; Kim, Bom Soo; Kim, Seung Min; Kim, Yu Mi; Kim, Hyong Nyun; Park, Jae Yong; Cho, Jae Ho; Choi, Youngrak	Pre-clinical trial	Low	Not serious	Not serious	Not serious	Not serious	N/A	No	High
Chen; Cai, Leyi; Zheng, Wenhao; Wang, Jianshun; Guo, Xiaoshan; Chen, Hua	Randomised control trial	Moderate	Not serious	Not serious	Some concerns	Not serious	N/A	No	High
Nie; Gu, Fei; Wang, Zhaojun; Wu, Rui; Yue, Yang; Shao, Anze	Retrospective case series	Moderate	Not serious	Not serious	Not serious	Not serious	N/A	No	Moderate
Wang; Hu, Jian; Guan, Junjie; Chen, Yunfeng; Wang, Lei	Retrospective study	High	Not serious	Not serious	Not serious	Some concerns	N/A	No	Moderate
Yang; Grottkau, Brian; He, Zhixu; Ye, Chuan	Randomised control trial	Moderate	Not serious	Not serious	Not serious	Some concerns	N/A	No	High

Supplementary table 2. Risk of bias assessment for randomised control trial using RoB2 tool

Item	Ozturk A.M.; Suer O.; Aktuglu K.; Derin O.; Ozer M.A.; Govsa F.	Yin H.-W.; Feng J.-T.; Yu B.-F.; Shen Y.-D.; Gu Y.-D.; Xu W.-D.	Hasan S.; Hamersveld K.T.V.; Mheen P.J.M.-V.; Kaptein B.L.; Nelissen R.G.H.H.; Toksvig-Larsen S.	Wang X.J.; Sun H.H.; Zhang Y.Y.; Yang R.Z.; Hao D.J.	Liu K.; Li Z.; Ma Y.; Lian H.	Wan L.; Zhang X.; Zhang S.; Li K.; Cao P.; Li J.; Wu G.	Ozturk; Suer, Onur; Derin, Okan; Ozer, Mehmet Asim; Govsa, Figen; Aktuglu, Kemal	Gang Yang; Jian Yu; Yanqing Zhou; Sujuan Li; Quanhui Zheng; Bing Zhang; Kong, Lingde; Yang, Gang; Yu, Jian; Zhou, Yanqing; Li, Sujuan; Zheng, Quanhui; Zhang, Bing	Chen; Cai, Leyi; Zheng, Wenhao; Wang, Jianshun; Guo, Xiaoshan; Chen, Hua	Yang; Grottkau, Brian; He, Zhixu; Ye, Chuan
Random sequence generation	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	Low risk
Allocation concealment to participant	High risk	High risk	Low risk	High risk	Low risk	Moderate risk	High risk	Low risk	Low risk	Moderate risk
Allocation concealment to researcher	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	High risk	High risk	High risk
Blinding of outcome assessment	High risk	Low risk	Low risk	High risk	Moderate risk	High risk	High risk	High risk	High risk	High risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Risk of bias	High	Low	Low	High	Low	High	High	Moderate	Moderate	Moderate

Supplementary table 3. Risk of bias assessments for non-randomised control trials using the ROBINS-I tool

Study	Confounding	Selection	Intervention Measurement	Missing Data	Outcome Measurement	Reported Results	Overall
Wang K.C.; Leong N.; Hasan S.A.; Siegel E.L.; Jones A.; Kambhampati S.; Shiu B.; Liacouras P.C.; Stuelke S.	Low	Moderate	Low	Low	High	Low	Moderate
Wang X.; Zhu Z.; Peng J.; Chen X. (chenxdmd@163.com); Liu S.; Zhang L.; Guan J.	Low	Moderate	Low	Low	High	Low	Moderate
Jovicic M.S.; Ribicic T.; Simunic S.; Vuletic F.; Petrovic T.; Kolundzic R. (robert.kolundzic@zg.t-com.hr)	Moderate	High	Low	Low	Moderate	Low	High
Punyaratabandhu T.; Pairojboriboon S.; Liacouras P.C.	Moderate	High	Low	Moderate	Moderate	Low	High
Wang X.J.; Sun H.H.; Zhang Y.Y.; Yang R.Z.; Hao D.J.	Low	Low	Low	Low	High	Low	Low
Wei F.; Li Z.; Liu Z.; Liu X.; Jiang L.; Yu M.; Xu N.; Wu F.; Dang L.; Zhou H.; Cai H.	Low	Moderate	Low	Low	Moderate	Low	Low
Angelini A.; Trovarelli G.; Ruggieri P.; Kotrych D.; Bohatyrewicz A.; Szafranski A.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Samaila E.M.; Negri S.; Maluta T.; Magnan B.; Zardini A.; Rossignoli C.; Bizzotto N.	Low	Moderate	Low	Low	High	Low	Moderate
Horas K.; Hoffmann R.; Faulenbach M.; Heinz S.M.; Schweigkofler U.; Langheinrich A.	Moderate	High	Moderate	Low	High	Low	High
Cai X.; Xu Y.; Yu K.; He X.; Luo H.; Duan J.; Wu Y.	Low	Moderate	Low	Low	Moderate	Low	Moderate
Park J.W.; Kang H.G. (ostumor@ncc.re.kr); Kim J.H.; Kim H.-S.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Huang J.-H.; Liao H.; Tan X.-Y.; Zhou Q.; Cao H.-Y.; Zeng C.-J.; Zheng Y.-S.; Xing W.-R.	Low	Low	Low	Low	High	Low	Low
Liu W.; Shao Z.; Hu B.; Wu Q.; Hu H.; Zhang S.; Wang B.; Rai S.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Hu H.; Liu W.; Wang S.; Zhang Z.; Liu J.; Shao Z. (szwpro@163.com); Wang B. (wangbaichuan-112@163.com); Zeng Q.; Zhang Y.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Mishra A.; Verma T.; Vaish A.; Vaish R.; Maini L.; Vaishya R.	Low	Moderate	Moderate	Moderate	Moderate	Moderate	High
Duan X.-J.; Fan H.-Q.; Wang F.-Y.; Yang L.; He P.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Wan J.; Zhang C.; Liu Y.-P.; He H.-B.	Low	Moderate	Low	Low	Moderate	Low	Moderate
Xu J.; Zhong S.; Huang W.; He Z.; Wei C.; Zheng Y.; Li W.; Zhang G.; Lin H.; Chen Y.	Moderate	Moderate	Low	Low	High	Low	High
Tracey J.; Arora D.; Gross C.E.; Parekh S.G.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Dekker T.J.; Steele J.R.; Federer A.E.; Hamid K.S.; Adams S.B.	Low	High	Low	Low	High	Low	Moderate
Girolami M.; Bandiera S.; Barbanti-Brodano G.; Ghermandi R.; Terzi S.; Tedesco G.; Evangelisti G.; Pipola V.; Gasbarrini A.; Boriani S.	Moderate	High	Low	Low	High	Moderate	High
Park J.W.; Kang H.G.; Kim J.H.; Park D.W.; Lim K.M.; Kim H.S.	Moderate	High	Low	Low	High	Low	High
Gorbatov R.O.; Malyshev E.E.; Romanov A.D.; Karyakin N.N.	Moderate	High	Low	Low	High	Low	High
Tian H.; Zhao M.-W.; Geng X.; Zhou Q.-Y.; Li Y.	Low	Moderate	Low	Low	High	Low	Moderate
Liu Y.; Zhou W.; Xia T.; Liu J.; Mi B.-B.; Hu L.-C.; Shao Z.-W.; Liu G.-H.	Low	Moderate	Low	Low	High	Low	Moderate
Wang Q.; Guan J.; Chen Y.; Wang L.; Hu J.	Low	Moderate	Low	Low	Moderate	Low	Moderate
Bauer A.S.; Storelli D.A.R.; Mccarroll H.R.; Lattanza L.L.; Sibbel S.E.	Low	Moderate	Low	Low	High	Low	High

Supplementary table 3. Continued

Zang C.-W.; Zhang J.-L.; Meng Z.-Z.; Liu L.-F.; Zhang W.-Z.; Chen Y.-X.; Cong R.	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Giannetti S.; Stancati A.; Santucci A.; Bizzotto N.	Low	Moderate	Low	Low	Moderate	Low	Moderate
Liang H.; Ji T.; Zhang Y.; Wang Y.; Guo W.	Low	Moderate	Low	Moderate	High	Low	High
Ma L.; Zhou Y.; Lin Z.; Chen L.; Xia H.; Zhu Y.; Mao C.; Zhang Y.	Low	High	Low	Low	Moderate	Low	Moderate
Luo W.; Huang L.; Liu H.; Qu W.; Zhao X.; Wang C.; Li C.; Yu T.; Han Q.; Wang J. (jinchengwang2015@gmail.com); Qin Y. (yanguoqin2015@gmail.com)	Moderate	Moderate	Low	Low	High	Low	High
Allan R.; Woodburn J.; Abbott M.; Steultjens M.P.; Telfer S.	Low	High	Low	Low	Low	Low	Low
Li H.; Qu X.; Mao Y.; Dai K.; Zhu Z. (zhenan_zhu@126.com)	Low	Low	Low	Low	High	Low	Moderate
Ma L.; Wang Y.; Zhou Y.; Zhu Y.; Mao C.; Lin Z.; Zhang Y.; Xia H.	Low	High	Low	Low	High	Low	Moderate
Storelli D.A.; Bauer A.S.; Lattanza L.L.; McCarroll H.R.	Moderate	High	Low	Low	High	Low	High
Ozturk A.M.; Suer O.; Coban I.; Ozer M.A.; Govsa F.	Moderate	High	Low	Low	High	Low	High
Nam H.-S.; Kim D.H.; Park D.-S.; Seo C.H.; Joo S.-Y.	Moderate	High	Low	Low	High	Low	High
Nie; Gu, Fei; Wang, Zhaojun; Wu, Rui; Yue, Yang; Shao, Anze	Low	High	Low	Low	High	Low	Moderate
Wang; Hu, Jian; Guan, Junjie; Chen, Yunfeng; Wang, Lei	Low	High	Moderate	Low	High	Low	High

Supplementary table 4. Risk of bias assessment of non-animal preclinical studies. We used the following domains:
Exposure - Was exposure status measured in a reliable, standardised way?
Outcome assessment - Were the outcome measures accurate? Were the outcome measures valid/reliable? Were the assessors of the outcomes blinded to the exposure status?
Confounders - were confounding variables described and accounted for?
Analysis - Were appropriate statistical measures used?
Selective reporting - Were all measured outcomes reported by the authors?
Conflict of interest - Were there any funding sources or conflicts of interest that may add bias to the authors' interpretation of the results?

Study	Exposure	Outcome assessment	Confounders	Analysis	Selective reporting	Conflict of interest	Risk of bias
Maier J.; Weiherer M.; Palm C.; Huber M.	Low	High	Low	Low	Low	Low	Low
Lipskas J.; Yao W.; Deep K.	Low	High	Low	Low	Low	Low	Low
Chen J.V.; Dang A.B.C.; Lee C.S.	Low	High	Low	Low	Moderate	High	Moderate
Hao J.; Wu Y.Y.; Rajaraman M.; Shimada K.; Nangunoori R.; Cook D.; Yu A.; Cheng B.	Low	High	Moderate	Low	Low	Moderate	Moderate
Farrell D.A.; Miller T.J.; Chambers J.R.; Joseph V.A.; McClellan W.T.	Moderate	High	Low	N/A*	Moderate	Low	High
Stefan P.; Pfandler M.; Lazarovici M.; Weigl M.; Navab N.; Euler E.; Furmetz J.; Weidert S.	Low	Moderate	Moderate	Low	Low	Low	Moderate
Tilton M.; Manogharan G.P.; Armstrong A.; Lewis G.S.; Sanville J.; Chin M.; Hast M.W.	Low	Low	Moderate	Low	Low	Moderate	Low
Blaya F.; Pedro P.S.; Lopez-Silva J.; D'Amato R.; Pedro A.B.S.; Juanes J.A.	Low	Moderate	Low	Low	Low	Low	Low
Javan R.; Ellenbogen A.L.; Haji-Momenian S.; Greek N.	Low	High	Low	Moderate	Moderate	Low	High
van Duren B.H.; Pandit H.; Lebe M.; Davies D.C.; Somashekar N.	Low	High	Moderate	Moderate	Low	Low	High
Tomazevic M.; Kristan A.; Cimerman M.; Kamath A.F.	Low	Moderate	Moderate	Low	Low	Low	Moderate

Supplementary table 4.Continued							
Cazon A.; Kelly S.; Paterson A.M.; Bibb R.J.; Campbell R.I.	Low	Moderate	Low	Moderate	Low	Low	Moderate
Burzynska K.; Filipiak J.; Morasiewicz P.	Low	High	Moderate	Moderate	Moderate	Low	High
Serra T.; Capelli C.; Toumpaniari R.; Orriss I.R.; Leong J.J.; Dalgarno K.; Kalaskar D.M.	Low	Moderate	Moderate	Low	Low	Moderate	Moderate
Kang; Kim, Bom Soo; Kim, Seung Min; Kim, Yu Mi; Kim, Hyong Nyun; Park, Jae Yong; Cho, Jae Ho; Choi, Youngrak	Low	Moderate	Low	Low	Low	Low	Low