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REVIEW ARTICLE

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Regeneration of alveolar bone defects in the experimental pig model: A systematic review and meta-analysis

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Abstract

Objective: Pigs are emerging as a preferred experimental in vivo model for bone regeneration. The study objective was to answer the focused PEO question: in the pig model (P), what is the capacity of experimental alveolar bone defects (E) for spontaneous regeneration in terms of new bone formation (O)?

Methods: Following PRISMA guidelines, electronic databases were searched for studies reporting experimental bone defects or extraction socket healing in the maxillae or mandibles of pigs. The main inclusion criteria were the presence of a control group of untreated defects/sockets and the assessment of regeneration via 3D tomography [radiographic defect fill (RDF)] or 2D histomorphometry [new bone formation (NBF)]. Random effects meta-analyses were performed for the outcomes RDF and NBF.

Results: Overall, 45 studies were included reporting on alveolar bone defects or extraction sockets, most frequently in the mandibles of minipigs. Based on morphology, defects were broadly classified as 'box-defects' (BD) or 'cylinder-defects' (CD) with a wide range of healing times (10 days to 52 weeks). Meta-analyses revealed pooled estimates (with 95% confidence intervals) of 50% RDF (36.87%–63.15%) and 43.74% NBF (30.47%–57%) in BD, and 44% RDF (16.48%–71.61%) and 39.67% NBF (31.53%–47.81%) in CD, which were similar to estimates of socket-healing [48.74% RDF (40.35%–57.13%) and 38.73% NBF (28.57%–48.89%)]. Heterogeneity in the meta-analysis was high ($I^2 > 90\%$).

Conclusion: A substantial body of literature revealed a high capacity for spontaneous regeneration in experimental alveolar bone defects of (mini)pigs, which should be considered in future studies of bone regeneration in this animal model.

KEYWORDS
animal models, bone regeneration, systematic reviews

1 | INTRODUCTION

The rehabilitation of edentulous areas with dental implants is a predictable tool, provided there is enough alveolar bone availability to allow for implant placement in adequate positions. However, this ideal bone environment frequently does not occur, and different bone regenerative interventions have been proposed to overcome this limitation (Sanz-Sanchez et al., 2015). Guided bone regeneration (GBR), based on the use of a bone replacement graft and a barrier membrane, has been the most tested intervention (Benic & Hammerle, 2014; Thoma et al., 2019; Urban et al., 2019); however, despite robust long-term evidence of efficacy, there are still some limitations regarding the bone replacement material especially in large defects, that is, autologous bone grafts (harvesting morbidity, rapid resorption rate) or its alternatives, that is, allogeneic, xenogeneic, and alloplastic bone substitutes (lack of osteogenic and/or osteoinductive capacity) (Gimbel et al., 2007). Consequently, novel strategies based on tissue engineering (growth factors and/or osteogenic cells) have been evaluated, mainly in large bone defects, to provide additional osteoinductive potential to the bone replacement grafts (Shanbhag et al., 2019).

Preclinical testing of new regenerative therapies in clinically relevant animal models is an important aspect of translational research and, in most cases, a requirement of regulatory health agencies before initiating human clinical trials (Pellegrini et al., 2009; Stavropoulos et al., 2015). While small-animal models (rodents and rabbits) usually constitute the starting point for proof-of-principle or feasibility studies, studies in large-animal models (dogs, pigs, sheep, and non-human primates) are needed to simulate clinical conditions, confirm the regenerative potential, and predict therapeutic efficacy (Stavropoulos et al., 2015). Furthermore, ISO standards (ISO 7405:2018) state that dental implants must be tested in an animal model in their final form prior to clinical use, and accordingly, large animals must be employed for such preclinical testing (Stadlinger et al., 2012).

Besides the biological and technical aspects, other economic, ethical, and cultural aspects may also play a vital role in the selection of an appropriate animal model. Although non-human primates (NHPs) represent the closest animal model to humans based on genetic background and biological similarity, the economic and ethical concerns surrounding their use have made this model almost completely non-viable in several countries (Pearce et al., 2007). Hence, dog, sheep, goat, and pig models are the preferred alternatives since their bone composition and biology are very similar to those of humans. From these, dog models are arguably the most frequently used in bone/biomaterial research (Marei et al., 2018; Wancket, 2015). However, like NHPs, their use in experimental in vivo investigations has raised significant criticisms given their role as companion animals. In fact, a recent survey showed that there is a perceived difference in moral status between companion animals and farm animals, such as pigs (Goni-Balentziaga et al., 2022). Since pigs are considered to be food-producing animals, their use may have the advantage of a relatively less critical public perception when used in experimental in vivo investigations. Additional advantages of their use are their easy availability, relatively low cost, ability to produce large litters, and the possibility to obtain a larger volume of tissue biopsies (Mardas et al., 2014; Rubessa et al., 2017; Stembirek et al., 2012; Wang et al., 2007). Furthermore, pigs are closely related to humans in terms of bone anatomy, composition, and metabolism (Mangione et al., 2022; Martiniaková et al., 2006; Pilawski et al., 2021). Thus, there is a growing trend towards 'phasing out' of dog models and promoting the use of pigs as the preclinical model of choice in bone regenerative studies.

The critical-size defect (CSD) is a widely used experimental model for screening bone biomaterials. A CSD is the smallest-size experimental defect that will not spontaneously and completely regenerate with bone in a defined timeframe without intervention (Hollinger & Kleinschmidt, 1990; Schmitz & Hollinger, 1986). Previous reviews of large-animal models have reported a large variation in bone defect models in terms of defect site, morphology, healing time, etc. (Marei et al., 2018; Shanbhag et al., 2016, 2018). In pigs, it is currently unclear which defect designs and dimensions most accurately represent a CSD in the alveolar bone (Mardas et al., 2014). It is important to determine the degree of spontaneous healing in an experimental defect model to obtain a reliable estimate of treatment efficacy (Schemitsch, 2017). Moreover, standardization of defect models is important to better reflect the clinical scenario, allow reliable comparisons across studies, and facilitate faster clinical translation of new therapies. Systematic reviews and meta-analyses of animal studies can be useful for detecting heterogeneity and improving the methodological quality of future studies (Hooijmans, IntHout, et al., 2014). Therefore, our objective was to systematically review the literature to answer the focused 'PEO' (population—exposure—outcome) question: in the pig model (P), what is the capacity of experimental alveolar bone defects (E) for spontaneous healing in terms of new bone formation (O)?

2 | METHODS

2.1 | Study design

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) and Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) guidelines (Leenaars et al., 2012) and registered on the PROSPERO: International Prospective Register of Systematic Reviews database (CRD42023450700).

Inclusion criteria:

1. Experimental in vivo studies in pigs, including minipigs.
2. Creation of experimental bone defects in the maxilla or mandible.
3. A control group of animals/defects receiving no treatment is labelled as 'sham', 'empty defect', or 'no treatment' group.
4. Quantitative assessment of spontaneous healing (new bone formation) in the defects using clinical measurements, tomography

[computerized tomography (CT), cone-beam CT (CBCT), micro-CT], and/or histomorphometry.

Exclusion criteria:

1. In vivo studies in other animal species.
2. In vivo studies reporting defects in other anatomical sites (calvarial or non-maxillofacial) and ectopic (subcutaneous or intramuscular implantation) models.
3. Absence of a control group with no treatment.
4. Reporting of only qualitative or semiquantitative radiographic and/or histological analyses.
5. In vitro and in silico studies
6. Clinical studies

Outcome: The primary outcome of interest was unassisted or spontaneous healing in control defects reported as three-dimensional (3D) radiographic/tomographic 'defect fill' (RDF), that is, new bone volume relative to the defect volume (BV/TV), or 2D histomorphometric new bone formation (NBF), that is, area of new bone or mineralized tissue (not including any biomaterial) relative to the total area of interest in histological sections.

2.2 | Search strategy, screening, and study selection

A search strategy was developed with assistance from the University of Bergen library in accordance with the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) guidelines (Leenaars et al., 2012). Electronic databases of MEDLINE (via PubMed), EMBASE, and Web of Science were searched for relevant literature up to and including July 2023 (Table S1). Bibliographies of the selected studies and relevant review articles were checked for cross-references, and additional relevant studies were obtained using the Google and Google Scholar search engines. Titles and abstracts of the search-identified studies were screened by two authors (S.S. and C.K.) and full texts of all eligible studies were obtained. Uncertainty in the determination of eligibility was resolved by discussion with the other authors. Two authors (S.S. and C.K.) reviewed the selected full texts independently and final inclusion was based on the aforementioned criteria. Inter-rater reliability was measured using the Cohen's kappa statistic. A flowchart for study selection is presented in Figure S1.

2.3 | Data extraction

Based on full-text screening of the selected studies, the following data was extracted using a standardized, pre-piloted form: author(s), study design, animal characteristics, model type, number of animals/defects, number of procedures, intervention(s), observation time(s), outcome(s), method(s) of outcome evaluation, main findings, and conclusions. Missing data was requested from the authors. Descriptive summaries of studies included were entered into tables. Quantitative radiographic and histomorphometric data was extracted for possible meta-analysis; data were recorded as (or converted into) means and standard deviations (SD) for analysis. If data were only expressed graphically, numerical values were requested from the authors, and if no response was received, a digital ruler software was used to measure graphical data (ImageJ; National Institutes of Health, Bethesda, MD, USA).

2.4 | Quality assessment and risk of bias

Reporting quality assessment of all studies will be performed based on a modification of the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines (Kilkenny et al., 2010), regarding relevant items (Berglundh & Stavropoulos, 2012). Compliance with the guidelines was evaluated using a predefined grading system applied to each of the 20 items (Schwarz et al., 2012) (Table S2). Reporting quality was judged as 'high', 'moderate', or 'low'. Risk of bias (RoB) assessment is performed using a modification of the SYRCLE RoB tool for animal studies, and judged as 'high', 'low', or 'unclear' (Hooijmans, Rovers, et al., 2014) (Table S3). Any disagreement between the reviewers during study selection, data extraction, and quality assessment was resolved by discussion and consensus.

2.5 | Meta-analysis

A meta-analysis was performed for the outcomes RDF and NBF using STATA Statistical Software 12 (StataCorp LP, College Station, TX, USA) and the DerSimonian and Laird random effects model, assuming some level of heterogeneity between data from the individual studies (Deeks et al., 2008). Studies were grouped based on defect type (BD, CD, or extraction sockets), and pooled estimates [effect sizes (ES)] were calculated along with 95% confidence intervals (CI). The I^2 statistic was used as a measure of heterogeneity across studies, with an $I^2 > 75\%$ indicating substantial heterogeneity (Deeks et al., 2008). Univariate meta-regression analyses were performed to test the effect of the following variables on the outcome in each category: model (minipig or domestic pig), age (months), jaw (mandible or maxilla), site (ridge, body, or angle/ramus), approach (intraoral or extraoral), periosteum (removed or preserved), membrane (used or not), defect volume, and observation time.

3 | RESULTS

3.1 | Search results

The initial search yielded 762 studies, which included all types of bone defects (i.e., segmental or continuity defects and non-segmental alveolar bone defects) and all types of regenerative

interventions (onlay/lateral/vertical augmentation, maxillary sinus augmentation, alveolar cleft repair, distraction osteogenesis, ridge preservation/socket grafting, ridge split, osteonecrosis, and peri-implant reconstruction) aimed at bone regeneration in pigs. To limit the scope of the review to the focused question, only those studies reporting non-segmental alveolar bone defects ($n = 143$ studies) were considered for inclusion [Cohen's $\kappa = 0.857$ (95% CI 0.811–0.903)]. We decided to use extraction sockets as a reference for 'natural' healing; therefore, studies reporting healing of untreated extraction sockets were also included. Based on further eligibility criteria and a full-text review, 45 studies reporting on experimental defects ($n = 39$) and/or socket healing ($n = 7$) in the mandible or maxilla were included in the review (Table 1). The majority of studies ($n = 25$) reported evaluation of tissue engineering, that is, cell- and/or growth factor-based, strategies, while 14 studies evaluated different biomaterials and six studies reported model development. The main reasons for exclusion were the absence of an untreated control group and/or reporting of only qualitative 2D radiographic or histological outcomes. A list of studies reporting relevant experimental models but not meeting the inclusion criteria is presented in Table 2.

3.2 | Animals

Most studies ($n = 35$) reported the use of minipigs, particularly of the Göttingen or Yucatan type, while the remaining studies used domestic or farm-breed pigs. On average, the pigs were mostly females, aged 19.48 ± 11 months (mean ± SD).

3.3 | Characteristics of alveolar bone defects

Based on their morphology, alveolar bone defects were broadly classified as:

- box- or saddle-type defects (BD, $n = 27$ studies), which were usually 'non-contained', that is, missing at least two surrounding bony walls, created by removing a segment of the alveolar bone, or
- cylindrical defects (CD, $n = 17$ studies), which were usually 'contained', that is, with all but one surrounding bony wall intact, created using a cylindrical trephine bur. In some cases, CD were also prepared as 'full thickness' or 'bicortical' defects.
- Additionally, six studies reporting unassisted healing of extraction sockets (premolar and/or molar teeth) in the maxilla and/or mandible (Kunert-Keil et al., 2015; Leventis et al., 2018; Li et al., 2023; Mu et al., 2018; Srisurang et al., 2014; Ticha et al., 2022; Wang et al., 2020) were included as a 'natural' reference for spontaneous bone healing.

The most common anatomical site was the mandibular alveolar ridge (premolar-molar region); other sites included the mandibular body and ramus/angle (Table 1). Most studies reported a split-mouth design, that is, bilateral defects. The size of BD ranged from 0.5 to 11 cm^3, while CD ranged from 3 to 25 mm in diameter with varying depths. Studies reported either an extraoral or intraoral surgical approach to create BD and CD. Five studies reported the use of a barrier membrane over BD (Emam et al., 2020; Raymond et al., 2021) or CD (Buser et al., 1998; Jensen et al., 2006; Sanri et al., 2021). Observation times in the included studies ranged from 4 to 24 weeks for BD and 10 days to 52 weeks for CD.

Based on a previously reported threshold, that is, >5 cm^3 (Henkel, Gerber, et al., 2005), two studies systematically aimed to determine the 'critical size' of bone defects, in the mandibular body of pigs (Sun et al., 2014) and alveolar ridge of minipigs (Ruehe et al., 2009). In the first study (Sun et al., 2014), full-thickness BD of ≥5 cm^3 were reported to be of critical size after 12 weeks in the mandibular 'posterior body' (angle/ramus region; 34% RDF), but not in the 'anterior body' (molar region); the latter defects were substantially healed (68% RDF) by 12 weeks. In the second study (Ruehe et al., 2009), full-thickness BD of 4 cm^3 and 10 cm^3 in the mandibular ridge (premolar-molar region) revealed up to 87% and 75% RDF, respectively, after 6 weeks, and were therefore not considered to be of critical size. In a more recent study (Duong et al., 2023), similar defects (5 cm^3 buccal BD in the mandibular ridge) revealed up to 87% RDF after 8 weeks; however, the authors reported adequate reduction of alveolar ridge volume to simulate a 'chronic' defect at the end of 8 weeks.

Six studies reported chronic type BD in the mandibular ($n = 5$; 2–4.5 cm long buccal defects) (Duong et al., 2023; Herford et al., 2012; Stricker et al., 2014; Yeo et al., 2012; Zambon et al., 2012) or maxillary alveolar ridge ($n = 1$; 2 cm long buccal defect) (Kauffmann et al., 2021). In all studies, tooth extraction and BD were performed in a preliminary surgery followed by a healing period (4–12 weeks) to allow 'chronification' (mimicking atrophic ridges) before application of the regenerative procedure.

Three studies systematically investigated the role of periosteum preservation versus removal on the healing of BD in the in the mandibular body (angle/ramus or molar region) (Sun et al., 2014), alveolar ridge (Duong et al., 2023), or posterior inferior border (Liu et al., 2014). Compared to defects where the periosteum was preserved, in the inferior border, periosteum removal resulted in more compromised healing and mandibular deviation after 24 weeks (Liu et al., 2014). In the alveolar ridge, periosteum removal resulted in more pronounced vertical bone loss and approximately 9% lower RDF after 8 weeks (Duong et al., 2023). In the mandibular angle and body (molar region), no significant effect of periosteum removal was observed (Sun et al., 2014).

3.4 | Spontaneous healing

None of the included studies reported complete healing, that is, 100% regeneration or restoration of defects to the original dimensions, suggesting that, according to strict definitions, all defects were of critical size. For studies reporting quantitative assessments of defect healing, a threshold of 50% (Schemitsch, 2017) was used

TABLE 1 Summary of included studies reporting alveolar bone defect or socket healing ($n = 45$).

Year	Study	Animal	Age	Jaw	*N*	Defect type	Dimensions (post-extraction/ additional healing time)	Bilateral, *n* per side	Observation time	Outcome
Ridge										
2009	Ruehe et al. (2009)	Göttingen	3 y	man	3	BD	1.9, 4.2, 10.1 cm^3 (28 w)	Y, 1–2	6 w	RDF
2009	Thoma et al. (2009)	Göttingen	18 m	man	16	CD	8 × 8 mm (12 w)	Y, 2	10 d–2 m	NBF
2012	Abarrategi et al. (2012)	Pigs		max	8	BD	1.5 × 1 × 1 cm	Y, 1	12 w	RDF
2012	Tiainen et al. (2012)	Göttingen	18–24 m	man	6	CD	4 × 10 mm	Y, 2	6 w	RDF
2014	Thoma et al. (2014)	Göttingen	18 m	man	11	CD	7 × 7 mm (20 w)	Y, 3	10–21 d	NBF
2015	Brockmeyer et al. (2015)	Göttingen	Adult	man	12	BD	20 × 8 × 8 mm (16 w)	Y, 1	4–12 w	NBF
2015	Catros et al. (2015)	Göttingen	18 m	man	14	CD	8 × 6 mm (26 w)	Y, 3	3 w	NBF
2017	Tröltzsch et al. (2017)	Minipigs		man	18	BD	2 × 1 cm (13 w)	Y, 1	4–13 w	NBF
2021	Gomez et al. (2021)	Göttingen	22 m	man	18	BD	15 × 8 × 8 mm (12 w)	Y, 2	4–12 w	RDF
2021	Raymond et al. (2021)	Landrace	6 m	man, max	8	BD[a]	10 × 12 mm (same[T])	Y, 2	6–12 w	RDF
2021	Kauffmann et al. (2021)	Minipigs	>2 y	max	18	BD[a]	2 × 1 cm (same[T], 3 m healing)	Y, 1	4–13 w	NBF
2021	Zhao et al. (2021)	Minipigs	10 m	max	12	BD	1 × 1.2 × 0.6 cm (NR)	Y, 2	12 w	RDF, NBF
2022	Ticha et al. (2022)	Yucatan	26–34 m	man	8	CD	3.3 mm dia. (12 w)	Y, 3	1–12 w	RDF
2022	Lau et al. (2022, 2023)	Domestic	Adult	man	5	BD	8 × 8 × 3 mm (12 w)	Y, 2	3 m	semi-RDF
2023	Duong et al. (2023)	Aachen	17–84 m	man	3	BD[a]	2.5 × 2 cm (same[T])	Y, 1	2 m	RDF
Body										
1982	Rosenquist et al. (1982)	Pigs	10 w	max	9	BD	8 × 8 mm	Y, 4	7 w	semi-NBF
2003	Gröger et al. (2003)	Göttingen	5–6 m	man	6	BD	20 × 10 mm	N, 1	90–180 d	semi-NBF
2004	Fuerst, Reinhard, et al. (2004)	Minipigs	Adult	man	8	CD	8 × 6 mm	Y, 3	4–8 w	NBF
2004	Fuerst, Gruber, et al. (2004)	Minipigs	Adult	man	8	CD	8 × 6 mm	Y, 3	4–8 w	NBF
2005	Henkel, Gerber, et al. (2005)	Göttingen	1 y	man	16	BD	5 cm^3 FT	N, 1	5 w	semi-NBF
2009	Zheng et al. (2009)	Minipigs	4–6 m	man	10	BD	2.5 × 1.5 × 1.5 cm	N, 1	24 w	RDF, NBF
2013	Tödtmann et al. (2013)	Minipigs		man	10	CD	10 × 3 mm	N, 7	4 m	NBF
2014	Sun et al. (2014)	Domestic	4 m	man	6	BD	3–5 cm^3	Y, 1	6–12 w	RDF
2014	Liu et al. (2014)	Minipigs	3 m	man	18	BD	3 × 1.5 cm FT	Y, 1	12–24 w	semi-RDF
2015	Konopnicki et al. (2015)	Yucatan		man	2	BD	2 × 2 cm	Y, 3	8 w	NBF
2016	Carlisle et al. (2016)	Sinclair	>1 y	man	5	BD	3 × 1 × 2 cm	Y, 1	4–16 w	RDF
2017	Scarano et al. (2017)	Minipigs	2 y	man	6	CD	5 × 5 mm	Y, 3	3 m	NBF

(Continues)

TABLE 1 (Continued)

Year	Study	Animal	Age	Jaw	*N*	Defect type	Dimensions (post-extraction/ additional healing time)	Bilateral, *n* per side	Observation time	Outcome
2018	Cui et al. (2018)	Minipigs	8–9 m	man	4	CD	10×5 mm	Y, 2	4 w	RDF
2020	Emam et al. (2020)	Domestic		man	6	BD	2×1 cm	Y, 3	12 w	RDF
Ramus/angle										
1997	Huang et al. (1997)	Minipigs		man	15	BD	15 cm^2	Y, 1	3, 6 w	semi-NBF
1998	Buser et al. (1998)	Minipigs	Adult	man	12	CD	12×10×12×5 mm	Y, 3	4–24 w	NBF
2002	Chu et al. (2002)	Yucatan	6 m	man	4	CD	8 mm FT	Y, 4	5–9 w	NBF
2009	Jensen et al. (2009)	Göttingen		man	24	CD	9×4 mm	Y, 3	4–52 w	NBF
2012	Wilson et al. (2012)	Yorkshire	Young	man	15	CD	10 mm FT	Y, 1	2–4 w	semi-RDF
2015	Kuo et al. (2015)	Lanyu pig	3 m	man	12	CD	6 mm dia.	NR	8 w	NBF
2015	Kang et al. (2015)	Minipigs	Mature	man	3	CD	1.2×0.5 cm	N, 4	4–8 w	semi-RDF
2020	Maki et al. (2020)	Yorkshire	1–3 y	man	12	CD	25 mm dia. FT	Y, 1	8 w	RDF, NBF
2021	Sanri et al. (2021)	Domestic	4.5 m	man	9	CD	10×5 mm	Y, 3	10 w	NBF
2022	Thygesen et al. (2022)	Göttingen		man	8	BD	30×24×5 mm	Y, 1	24 w	semi-RDF
Extraction sockets							*Site*			
2014	Srisurang et al. (2014)	Minipigs	15 m	man, max	6		P2, P4	Y, 2	6–12 w	NBF
2015	Kunert-Keil et al. (2015)	Domestic	15 m	man	20		P3	Y, 1	4–12 w	NBF
2018	Mu et al. (2018)	Domestic	3 m	man	5		dm3	Y, 1	6 w	NBF
2018	Leventis et al. (2018)	Landrace	4 m	max	7		dm2	Y, 1	12 w	NBF
2020	Wang et al. (2020)	Minipigs	12 m	man	5		C	Y	1–2 m	RDF
2022	Ticha et al. (2022)	Yucatan	26–34 m	man	8		P	Y, 3	5–12 w	RDF
2023	Li et al. (2023)	Minipigs	2 y	man, max	8		P2, P4	Y, 2	6 m	RDF

Abbreviations: BD, box defects; C, canine; CD, cylinder defects; dia., diameter; dm, deciduous molar; FT, full thickness; m, months; man, mandible; max, maxilla; NBF, histomorphometric new bone formation; P, premolar; RDF, radiographic defect fill; T, simultaneous tooth extraction and defect creation; w, weeks; y, years; Y, yes.

[a]Chronic type defects.

TABLE 2 List of excluded studies reporting alveolar bone defect or socket healing.

Year	Study	Defect type	Size	Time	Reason for exclusion		
					No control group	Qualitative outcome	Other
Ridge							
1991	Schliephake et al. (1991)	BD	25×7×10 mm	5 m	Y		
1998	Jensen et al. (1998)	BD	10×10 mm	2–4 d	Y	Y	
2002	Pogrel et al. (2002)	BD	3×2 cm	3 m	Y	Y	
2004	Olsen et al. (2004)	BD	30×10 mm	3 m		Y	
2008	Tschon et al. (2009)	BD	3×4×15 mm	15–60 d	Y		
2009	Pieri et al. (2009)	CD	3.5 dia.×8 mm	3 m	Y		
2012	Herford et al. (2012) and Herford and Cicciu (2012)	BD	30×20 mm	3 m, 4 w	Y	Y	
2012	Zambon et al. (2012)	BD	40×6 mm	12 w		Y	
2012	Yeo et al. (2012)	BD	45×12×5 mm	8 w		Y	
2013	Stricker et al. (2014)	BD	Buccal wall removed (P2-M1)	12 w		Y	
2014	Clozza et al. (2014)	BD	10×10×10 mm	3, 8 w	Y		
2015	Dahlin et al. (2015)	CD	7 dia.×7 mm	3, 8 w	Y		
2017	Zhu et al. (2017)	CD	5 dia.×15 mm	12 w	Y	Y	
2019	de Carvalho et al. (2019)	CD	5 dia.×7 mm	3 m	Y		
2020	Wu et al. (2020)	CD	4 dia.×8 mm	6, 12 w	Y		
2020	Mihatovic et al. (2020)	CD	6 dia.×6 mm	20 w			Implants
2020	Steiner et al. (2021)	CD	7 mm dia.	12 w	Y		
2020	Karl et al. (2020)	CD	6 mm dia.	12, 18, 24 w	Y		
2021	Baek et al. (2015)	BD CD	5×10 mm FT 4 dia. ×8 mm	4, 8 w		Y	
2022	Unnikrishnan et al. (2022)	BD	3×2×1 cm	6 m	Y		
Body							
1992	Ouhayoun et al. (1992)	BD	5×5 mm	1 w–1 y		Y	
1998	Schliephake et al. (1998)	BD	2–4 cm	5 m		Y	
2005	Henkel et al. (2006) and Henkel, Bienengräber, et al. (2005)	BD	>5 cm^3	8 m	Y		
2005	Strietzel et al. (2006)	CD	4 dia. ×8 mm	4, 8, 12 w		Y	
2005	Meyer et al. (2012)	CD	4 cm dia.	3, 30 d	Y	Y	
2008	Mai, Reinstorf, et al. (2008)	CD	10 mm dia.	1–18 m		Y	
2008	Mai, Lux, et al. (2008)	CD	10 dia. ×4 mm	4 m		Y	
2009	Abukawa et al. (2009)	BD	2×2 cm	12, 20 w	Y	Y	
2009	Zhang et al. (2009)	BD	2×2 cm	12, 20 w	Y		
2009	Chang et al. (2009)	CD	2.5×1.5×1.4 cm	5 w, 8 m		Y	
2010	von Wilmowsky et al. (2010)	BD	3×2.5 cm	120 d	Y		
2016	Dau et al. (2016)	BD	2.5×1.5×1.4 cm	5 w, 8 m	Y		
2017	Tomco et al. (2017)	BD	4×2×2 mm	3, 9 w	Y	Y	
2019	Shi et al. (2019)	CD	12 dia. ×5 mm	2 m	Y		

(Continues)

TABLE 2 (Continued)

Year	Study	Defect type	Size	Time	Reason for exclusion		
					No control group	Qualitative outcome	Other
2019	Zhang et al. (2019)	BD	6×4.5×1.5 cm	4 m	Y		
2020	Bozo et al. (2020)	BD	25×15×10 mm	3, 6 m	Y		
2020	Probst et al. (2020)	BD	3×2×1 cm	12 w	Y		
2020	van Oirschot et al. (2020, 2022, 2023)	CD	8 dia. ×4 mm	4–12 w	Y		
2021	Djordjević et al. (2021)	CD	10 mm dia.	12 w	Y		
2022	Addis et al. (2022)	CD	5 dia. ×5 mm	1, 3 m	Y		
2022	Stevanovic et al. (2022)	BD	10×5 mm	4 m	Y		
2023	Vdoviaková et al. (2023)	BD	15×7×3 mm	3–6 m	Y		
Angle/ramus							
2002	Chu et al. (2002)	CD	8 mm dia. FT	5–9 w		Y	
2006	Jensen et al. (2006)	CD	9 dia. ×5 mm	1–24 w	Y		
2015	Jensen et al. (2015)	CD	NR	4–52 w		Y	
2009	López-López et al. (2009)	CD	3.8 dia. ×8 mm	2 m		Y	
2010	Lan Levengood et al. (2010)	CD	5 mm dia.	3–24 w	Y		
2011	Jensen et al. (2011)	CD	9 dia. ×5 mm	1–24 w	Y		
2011	Polak et al. (2011)	CD	5 mm dia.	3–24 w	Y		
2011	Lee et al. (2011, 2013)	CD	15 dia. ×5 mm	12 w	Y	Y	
2013	Liao et al. (2013)	BD	3×3 cm	3–6 m	Y		
2013	Hoekstra et al. (2013)	CD	7 mm dia.	4, 12 w	Y		
2014	Broggini et al. (2015)	CD	7 dia. ×4 mm	2–8 w	Y		
2015	Saulacic et al. (2015)	CD	7 dia. ×4 mm	1–8 w	Y		
2016	Tee et al. (2016)	BD	3.5×1.5×1 cm	12 w	Y		
2017	Weisgerber et al. (2018)	CD	10 mm dia. FT	6 w	Y		
2017	Lee et al. (2017)	CD	10 dia. ×3 mm	4–106 w	Y		
2018	Jung et al. (2018)	CD	10 dia. ×4 mm	3–9 w	Y		
2018	Kim et al. (2018)	CD	12 dia. ×4 mm	4–12 w	Y		
2021	Bouyer et al. (2021)	BD	4×3×1 cm FT	13 w			1 defect
2022	Dewey et al. (2021)	CD	25 dia. ×10 mm	8, 16 w	Y		
Extraction sockets							
2007	Oltramari, de Lima Navarro, et al. (2007) and Oltramari, Navarro, et al. (2007)		m4, P4	3 m		Y	
2020	Kauffmann et al. (2020)		P	16 w	Y		

Abbreviations: BD, box defects; CD, cylinder defects; dia., diameter; dm, deciduous molar; FT, full thickness; m, months; max, maxilla; man, mandible; P, premolar; w, weeks; y, years; Y, yes.

to categorize BD and CD, that is, defects showing > or ≤50% RDF or NBF, during the corresponding observation periods (Tables 3 and 4).

3.5 | Meta-analysis

A meta-analysis was separately performed for the outcomes RDF ($n=10$ studies) and NBF ($n=18$ studies); in each case, sub-groups were defined based on defect type, that is, BD and CD (Figures 1 and 2). Overall, the pooled estimates of spontaneous regeneration [ES (95% CI)] were as follows: 50% RDF (36.87%–63.15%) and 43.74% NBF (30.47%–57%) for BD, and 44% RDF (16.48%–71.61%) and 39.67% NBF (31.53%–47.81%) for CD. The corresponding estimates of spontaneous healing in extraction sockets were 48.74% RDF (40.35%–57.13%; $n=3$ studies) and 38.73% NBF (28.57%–48.89%; $n=4$ studies) (Figure 3). Univariate meta-regression analyses were

TABLE 3 Studies reporting tomographic outcomes.

Study				<50%	>50%
Alveolar defects	**Defect type**	**Size**	**Time**	**RDF**	**RDF**
Ridge, mandible					
Ruehe et al. (2009)	BD, FT	1.7×1.4×0.8 cm (~2 cm^3)	6 w		57.4
		2.0×1.4×1.5 cm (~4 cm^3)	6 w		87.2
		4.6×1.3×1.7 cm (~10 cm^3)	6 w		75.5
Duong et al. (2023)	BD, buccal	2.5×2 cm, PO removed	8 w		79.7
		2.5×2 cm, PO preserved	8w		87.9
Gomez et al. (2021)	BD, buccal	15×8×8 mm	4 w	5.2	
			8 w	38	
			12 w		53.9
Tiainen et al. (2012)	CD, socket	4×10 mm	6 w		73.6
Ticha et al. (2022)	CD	3.3 mm dia.	5 w	38.4	
			12 w		56.6
Ridge, maxilla					
Zhao et al. (2021)	BD, buccal	1×1.2×0.6 cm	12 w		58
Body, mandible					
Sun et al. (2014)	BD, molar region	3–5 cm^3 FT	6 w	42	
			12 w		68
Carlisle et al. (2016)	BD, inferior	3×1×2 cm FT	4 w	5	
			16 w	36.4	
Emam et al. (2020)	BD, posterior[a]	2×1 cm FT	12 w	48.8	
Angle/ramus					
Sun et al. (2014)	BD	3–5 cm^3 FT	6 w	21	
			12 w	34	
Maki et al. (2020)	CD	25 mm dia. FT	8 w	8	
Extraction sockets	Jaw	Site			
Ticha et al. (2022)	man	P	5 w	35	
			12 w		50.3
Li et al. (2023)	man, max	P2, P4	12 w	44	
			24 w		53
Wang et al. (2020)	man	C	8 w		60.7

Abbreviations: BD, box defects; C, canine; CD, cylinder defects; dia., diameter; FT, full thickness; P, premolar; PO, periosteum; RDF, radiographic defect fill.

[a]Membrane.

performed within each outcome group to test the effect of several factors. A significant positive effect of 'observation time' was found for (a) RDF in BD, that is, increasing RDF with time (4–8 w and 9–12 w vs. <4 w; $p < .005$), and (b) NBF in CD (>12 w vs. <4 w; $p < .001$) (Table S4). With regards to defect size (volume), a positive significant effect of increasing defect size was observed on NBF in BD (0.25–0.4 cm^3 vs. <0.25 cm^3; $p = .03$) (Table S5). Among the remaining variables, only age revealed a significant positive effect (increasing ES with increase in age) for RDF in BD ($p = .003$) (Table S6). Since multiple variables did not reveal significant results, a multivariate regression analysis was not performed. All meta-analyses revealed high heterogeneity ($I^2 > 90\%$) indicating that the corresponding results must be interpreted with caution. This was further confirmed by funnel plots, which revealed large variation among studies and potential publication bias (Figures S2 and S3).

3.6 | Quality assessment and risk of bias

On average, the overall quality of the included studies was judged to be average, and the RoB was judged to be moderate (Tables S7 and S8). For RoB, the items that most often scored poorly were related to baseline data, housing, blinding of operators, and blinding of assessors. It must be noted that the included studies covered a wide span of publication dates, with many studies being published before the ARRIVE and SYRCLE guidelines. Nevertheless, a clear need for

TABLE 4 Studies reporting histomorphometric outcomes.

Study				<50%	>50%
Alveolar defects	**Defect type**	**Size**	**Time**	**NBF**	**NBF**
Ridge, mandible					
Brockmeyer et al. (2015)	BD, buccal	20×8×8 mm	4 w	26	
			12 w	44	
Tröltzsch et al. (2017)	BD	2×1 cm FT	4 w	47.5	
			13 w		83.9
Catros et al. (2015)	CD	8×6 mm	3 w	22	
Thoma et al. (2009)[b]	CD	8×8 mm	3 w	18.3	
			8 w		52.3
Thoma et al. (2014)[b]	CD	7×7 mm	3 w		51.3
Ridge, maxilla					
Kauffmann et al. (2020)	BD, buccal	2×1 cm	16 w		54.6
			25 w		51.8
Zhao et al. (2021)	BD	1×1.2×0.6 cm	12 w	22	
Body, mandible					
Konopnicki et al. (2015)	BD, inferior	2×2 cm FT	8 w	35	
Zheng et al. (2009)	BD, anterior	2.5×1.5×1.5 cm FT	24 w	28.4	
Scarano et al. (2017)	CD, posterior	5×5 mm	12 w	23	
Fuerst, Reinhard, et al. (2004) and Fuerst, Gruber, et al. (2004)	CD, posterior	8×6 mm	4 w	13–14	
			8 w		54.2
Tödtmann et al. (2013)	CD, anterior	10×3 mm	16 w		64.7
Angle/ramus					
Buser et al. (1998)	CD[a]	12×10×5 mm	4 w	33.8	
			12 w		62.2
			24 w		55.3
Kuo et al. (2015)	CD	6 mm dia.	8 w	27	
Jensen et al. (2009)	CD[a]	9×4 mm	4 w	42.5	
			13 w		61.4
			26 w		57.6
			52 w	46.2	
Sanri et al. (2021)	CD[a]	10×5 mm	10 w	29.5	
Maki et al. (2020)	CD	25 mm dia. FT	8 w	11.3	
Extraction sockets	Jaw	Site			
Leventis et al. (2018)	max	dm2	12 w	15.4	
Mu et al. (2018)	man	dm3	6 w		51.6
Kunert-Keil et al. (2015)	man	P3	4 w	39.5	
			12 w	45.3	
Srisurang et al. (2014)	man, max	P2, P4	6 w	39.6	
			12 w	42.7	

Abbreviations: BD, box defects; CD, cylinder defects; dia., diameter; dm, deciduous molar; FT, full thickness; NBF, new bone formation; P, premolar.

[a]Membrane.

[b]Shortest obs. time (10 d) was excluded.

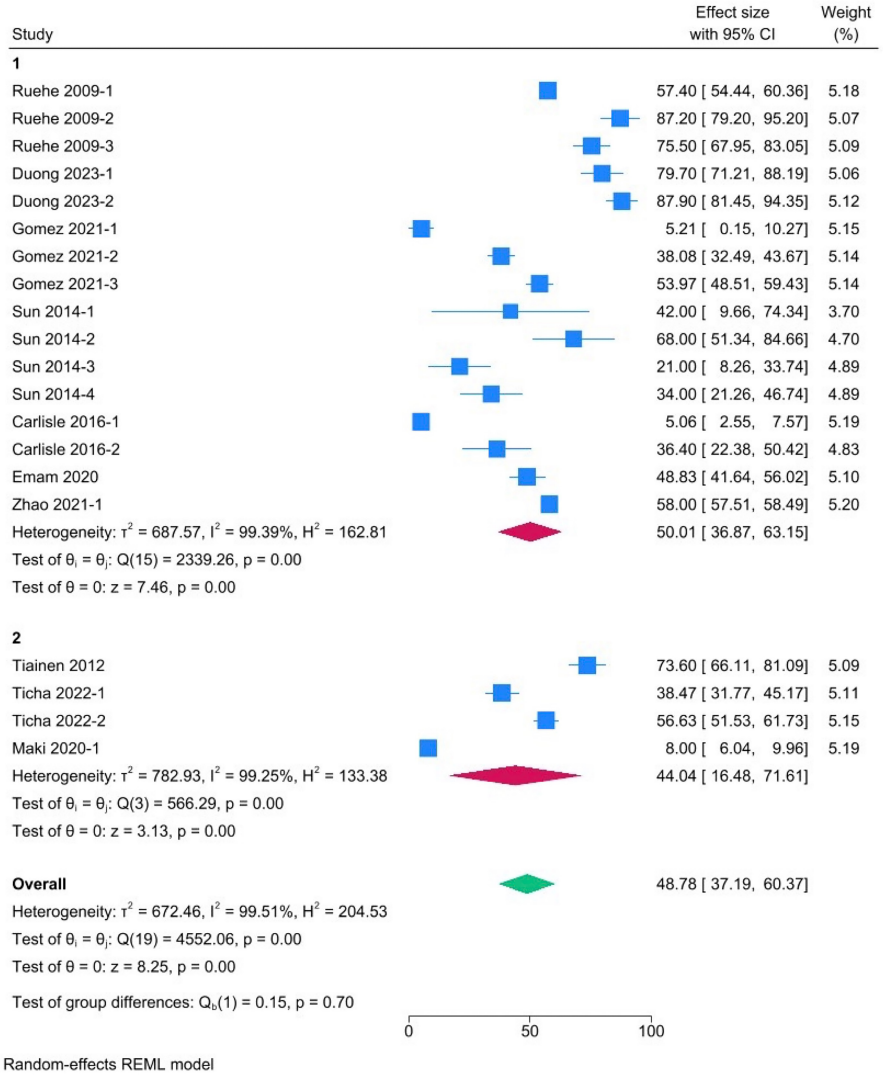

FIGURE 1 Meta-analysis of studies reporting tomographic outcomes (1 = box defects, 2 = cylinder defects).

better quality reporting and compliance with these guidelines was identified herein.

4 | DISCUSSION

The aim of this study was to systematically review the available scientific evidence to identify the most pertinent experimental design for alveolar bone regeneration using the pig as the experimental animal. Overall, a substantial number of relevant studies were identified, albeit with a large heterogeneity across studies in terms of the different model characteristics. The experimental defects were produced mainly in minipigs and located most frequently in the mandibular alveolar ridge, followed by the mandibular body and angle/ramus. Their shape could be broadly classified as box-type defects (BD) or cylindrical-type defects (CD). No studies reported complete, that is, 100%, spontaneous healing of alveolar BD or CD during the corresponding observation period, and therefore, according to strict definitions, these defects may be of critical size. However, based on our meta-analysis, the pig model demonstrated a high capacity for spontaneous alveolar bone regeneration, similar to the 'natural' healing observed in extraction sockets.

The optimal animal model for evaluating bone regenerative therapies should: (1) allow the application of a specific therapy in the same manner in which it will be delivered in a clinical setting, (2) offer an anatomical site that is closely matched to the most common clinical indication, (3) allow the use of surgical techniques that match the clinical methods, (4) provide a metabolic and physiological profile that is comparable to humans, and (5) allow the use of similar formulations of the therapy (composition, dose, degradation, etc.) as would be used clinically (Muschler et al., 2010). Indeed, pigs fulfil these criteria since they are closely related to humans in terms of bone anatomy, composition, and metabolism, and therefore, represent an optimal model of bone regeneration. A further advantage in using pig jaws is the possibility of using clinically relevant dimensions of dental implants and biomaterial scaffolds (Musskopf et al., 2022). Most of the included studies reported the use of minipigs, particularly Göttingen minipigs, on average 19–20 months

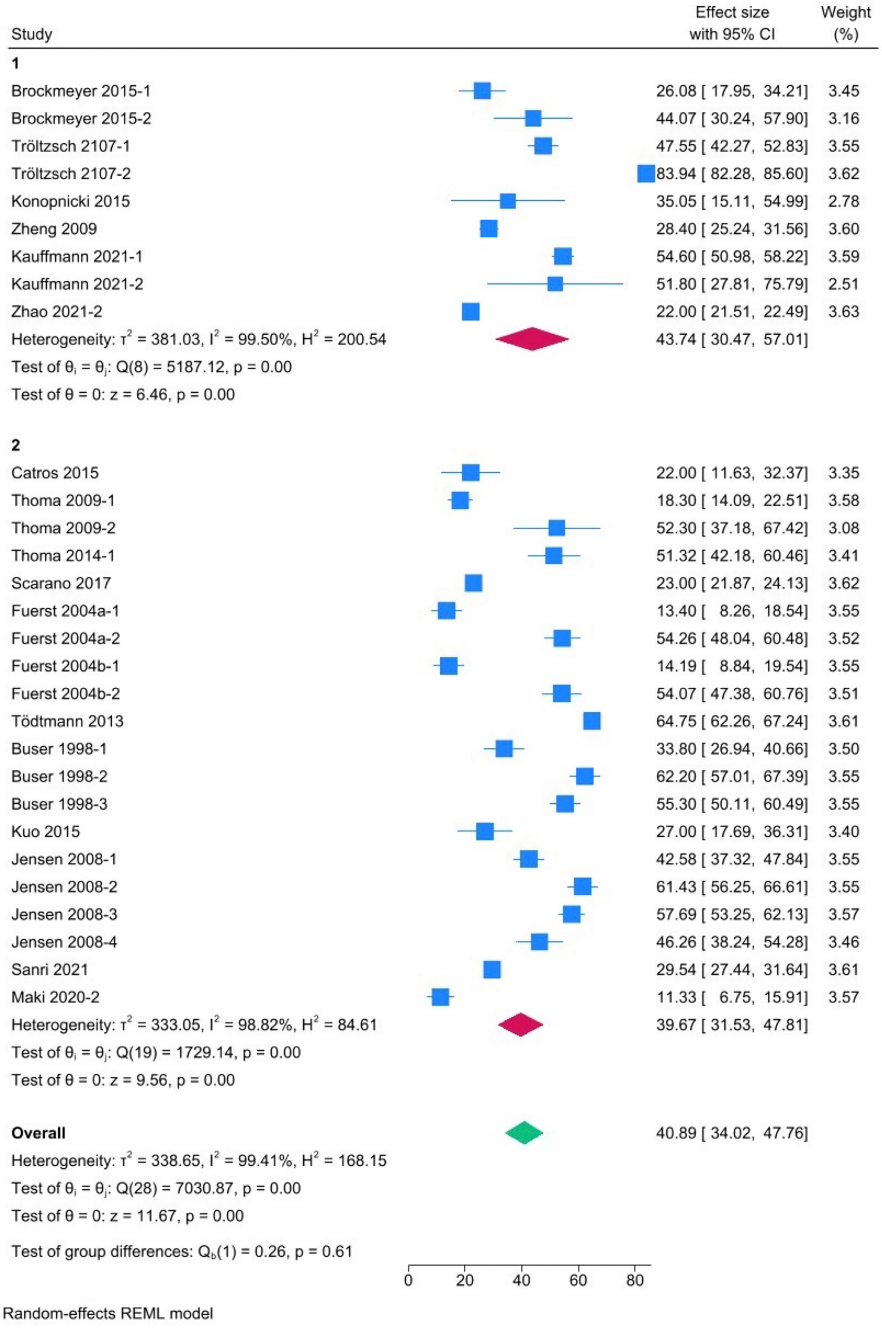

FIGURE 2 Meta-analysis of studies reporting histomorphometric outcomes (1 = box defects, 2 = cylinder defects).

old. In general, minipigs are reported to be more morphologically similar to humans in terms of skeletal features than lager farm breeds and have a more similar rate of mandibular bone regeneration (1.2–1.5 mm/day) to humans (1.0–1.5 mm/day) than do dogs (1.5–2.0 mm/day) (Kragstrup et al., 1989; Laiblin & Jaeschke, 1979). Moreover, several biological features of minipig alveolar bone, such as bone volume, and density are reported to be similar to those of humans (Pilawski et al., 2021). In the present analysis, the age of the animals revealed a significant effect on defect healing. The age of the animals could be an important factor, not only in terms of bone metabolism/turnover, but also dental eruption status since extractions of premolar/molar teeth are invariably necessary prior to defect creation in the alveolar ridge. Pigs have a diphyodont dentition comparable to that of humans (I-3, C, P-4, M-3) with all permanent teeth erupted by 14–23 months (Ide et al., 2013; Weaver et al., 1969); slightly earlier eruption times are reported in domestic versus miniature pigs (Davies, 1990). Given the high capacity for spontaneous healing, and accordingly, the need to create relatively large bone defects of 'critical size', it may be prudent to use mature (but not aged) animals with fully erupted dentitions.

In experimental in vivo investigations in bone regeneration, one of the most relevant confounding factors is the

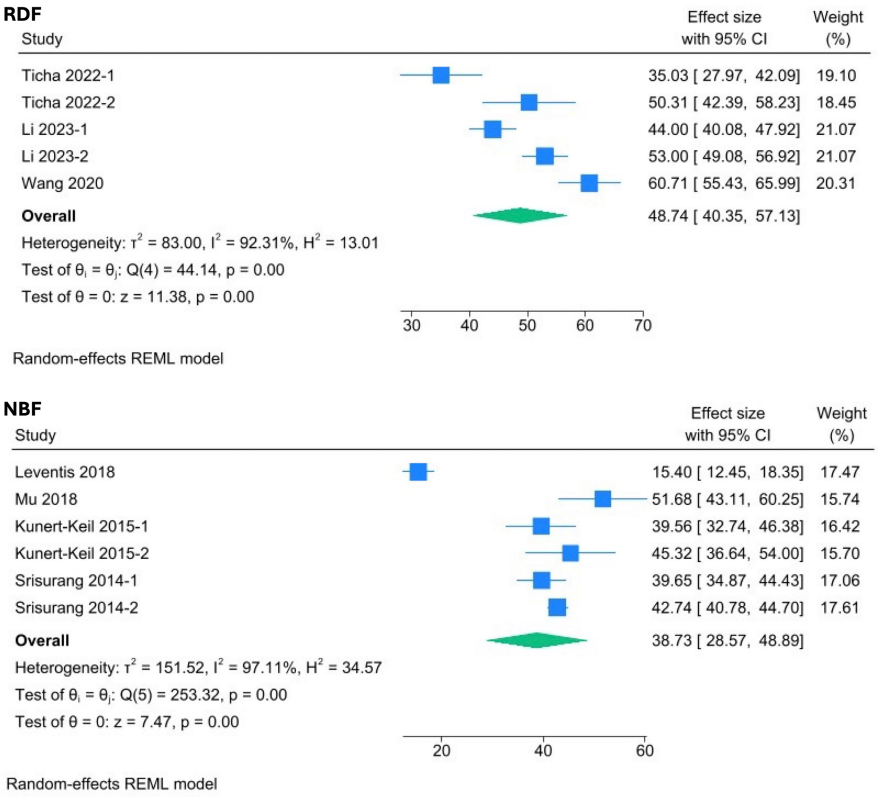

FIGURE 3 Meta-analysis of studies reporting healing of extraction sockets. NBF, new bone formation; RDF, radiographic defect fill.

self-regenerative potential of the animal model, and hence, the use of CSD, defined as the smallest-size experimental defect that will not spontaneously and completely regenerate with bone in a defined timeframe without intervention, is very relevant (Hollinger & Kleinschmidt, 1990; Schmitz & Hollinger, 1986). The features of CSD are specific to the animal model (depending on metabolic status and regenerative capacity) and the anatomical site (depending on the embryonic origin, e.g., long bones, calvaria, alveolar bone, etc.) (Reichert et al., 2009). However, several defect designs and dimensions may fulfil the definition of CSD, and additional confounding factors, for example, mechanical loading during healing, may complicate comparisons across studies (Schemitsch, 2017). In the present review, a wide range of dimensions for BD (0.5–10 cm^3 volume) and CD (3–25 mm diameter) were observed. One of the most frequently used 'thresholds' for CSD in minipigs is that of ≥5 cm^3 proposed by Henkel, Gerber, et al. (2005), originally as full-thickness BD in the mandibular parasymphysis. However, Ruehe et al. (2009) questioned the relevance of this threshold for alveolar ridge defects, by demonstrating up to 75.5% RDF in BD twice as large (10 cm^3) after 6 weeks. Similarly, Duong et al. (2023) reported up to 87% RDF in 'chronic' mandibular buccal BD of ≥5 cm^3 after 8 weeks. Furthermore, Sun et al. (2014) reported notable differences in spontaneous healing between full-thickness defects in the 'anterior' (molar region; 67% volume reduction) and 'posterior' mandibular body (angle region; 32% volume reduction) after 12 weeks. Therefore, it is also important to estimate the degree of spontaneous regeneration in a particular CSD model so as to: (a) not overestimate the effect of a particular treatment; and (b) detect clinically meaningful differences between experimental treatments (not masked by spontaneous healing) (Schemitsch, 2017).

Within CSDs, a distinction can be made between 'acute' defects (one-stage), which are created in the same surgery where bone regeneration is performed, and 'chronic' defects (two-stage), which allow for healing of the defect before a regenerative approach is performed. The latter method not only eliminates the confounding effect of any 'self-regeneration' potential from the tested approach but also results in a chronic defect mimicking the clinical scenario of atrophic ridges, for example, Class 4 or 5 defects according to the classification by Benic and Hämmerle (2014). Moreover, in acute type defects, the high degree of spontaneous regeneration may confound the detection of clinically meaningful differences between the tested therapies. Indeed, previous studies have reported similar amounts of bone formation in acute defects vs. extraction sockets following spontaneous regeneration (Ticha et al., 2022) or grafting (Steiner et al., 2021) in minipigs. Chronic defects have been frequently applied in the dog model to test GBR strategies (Sanz et al., 2017; Thieu et al., 2021). In the present review, studies reporting chronic mandibular defects were identified in minipigs, although five of these were excluded for not reporting quantitative outcomes. In all studies, tooth extraction and defect

creation was achieved in an initial surgical procedure followed by a healing period of 4–12 weeks to allow 'chronification' of the defects, before application of the regenerative therapy. The efficacy of the experimental model was confirmed upon surgical re-entry, whereby, despite a high degree of spontaneous healing (Duong et al., 2023), the authors observed adequate reductions in ridge dimensions to necessitate regeneration. Moreover, all studies reporting chronic ridge defects used an intraoral surgical approach with minimal or no complications during the healing phase. Indeed, other studies have reported severe complications, such as wound dehiscence and loss of graft materials, when using an intraoral approach in the minipig mandible (Jensen et al., 1998; Olsen et al., 2004). This has been attributed to the oral habits of pigs, such as continuous chewing on cages and other objects during the healing period, thus compromising wound stability. Nevertheless, while an extraoral approach may help to reduce the incidence of such complications, the clinical relevance of the surgical technique, and the translational value of the obtained results are superior when using an intraoral approach.

It is important to interpret the results of the present review in the context of the quality of the included studies and the heterogeneity between them. A relatively large variation in the location, size, and morphology of bone defects was observed between studies, which could likely have contributed to heterogeneity in the present meta-analysis. Indeed, previous studies have highlighted the influence of defect characteristics, such as site (e.g., 'marrow-rich' vs. 'marrow-poor' sites) (Guo et al., 2012), preservation or removal of bony cortices (e.g., 'partial-thickness' vs. 'full-thickness' defects) (Young et al., 2008) and preservation or removal of the periosteum (Ma et al., 2009) on regenerative outcomes. Reliability of the results also depends on the quality of the primary studies (Hooijmans, IntHout, et al., 2014). The overall methodological quality of the studies included, as assessed by compliance with the ARRIVE guidelines (Kilkenny et al., 2010), was found to be moderate. Standardization of defect models to better represent the clinical scenario and better study reporting should be important considerations in future preclinical studies of alveolar bone regeneration.

Unlike clinical meta-analyses, which aim to obtain a combined estimate or size of treatment effect, meta-analyses of preclinical studies aim to summarize the effect of an intervention, where the direction rather than size is meaningful, because of the large inherent variations in animal studies (Hooijmans, IntHout, et al., 2014; Vesterinen et al., 2014). Moreover, in the context of CSD, uniform defects are surgically created in healthy animals with sound surrounding tissues and a generally uncompromised blood supply, which is often not the case in clinical scenarios (Muschler et al., 2010). Thus, meta-analyses of animal studies tend to be exploratory rather than confirmatory. Accordingly, rather than emphasizing the specific estimates of RDF/NBF, the results herein may be interpreted as indicating a generally high capacity for spontaneous regeneration of alveolar bone defects in the pig model. Nevertheless, based on these data, the following factors may be considered when selecting the pig as an experimental model;

- The mandibular alveolar ridge (intraoral approach) may represent a more clinically relevant site for experimental regeneration as compared to the inferior body or angle/ramus region (extraoral approach). Minor complications, such as wound dehiscence, may be expected when performing large augmentations via an intraoral approach.
- Given the high capacity for spontaneous regeneration, box defects (resection) may be preferred over cylindrical defects (trephination), and chronic defects (two-stage) may be preferred over acute defects (one-stage), to mimic atrophic ridges.
- Based on limited data, posterior positioning and periosteum removal may mitigate spontaneous regeneration in mandibular defects.

5 | CONCLUSIONS

Based on our inclusion criteria, we identified 39 studies evaluating regeneration in experimental alveolar bone defects in the pig model. The results are derived mainly from mandibular defects in adult female Göttingen minipigs. Based on morphology, defects could be broadly classified as box- (usually 'non-contained') or cylinder-shaped (usually 'contained'). Overall, our meta-analysis revealed a high degree of spontaneous regeneration in untreated box- and cylinder-type defects, similar to that of extraction sockets in this animal model, albeit with a high heterogeneity. A tendency for increased regeneration was observed with longer observation times. Further well-designed studies and clearer definitions are needed to determine 'true' CSD in the alveolar bone of pig/minipig models.

AUTHOR CONTRIBUTIONS

S.S, J.S.E, and M.S. conceived and designed the study. S.S. and C.K. performed the review. S.A.L. performed the meta-analysis. S.S., C.K., J.S.E., M.S., R.G., K.M., and S.A.L. contributed to writing the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

DATA AVAILABILITY STATEMENT

Additional data are included in the Supplementary data file and can be made available by the authors upon reasonable request.

REGISTRATION

The review was prospectively registered on PROSPERO: International Prospective Register of Systematic Reviews database (CRD42023450700).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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