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Original Research

The translation of surgical animal models to human clinical research: A cross-sectional study

Yongle Ruan[1], N. Bryce Robinson[1], Faiza M. Khan, Irbaz Hameed, Mohamed Rahouma, Ajita Naik, Christian T. Oakley, Lisa Rong, Leonard N. Girardi, Mario Gaudino*

Department of Cardiothoracic Surgery, Weill Cornell Medical Center, 535 E 68th Street, New York, NY, 10065, USA

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ABSTRACT

Background: Surgical animal models are used in pre-clinical scientific studies. To date there has not been an analysis of how effective these data are when translated to human/clinical research. In this retrospective review, we evaluate the impact of studies using surgical animal models on human/clinical research through study-level analysis of citations.

Methods: The top two ranking clinical journals based on impact factor for the top ten surgical specialties were identified and a search was run on PubMed to identify studies using surgical animal models published in the years 2007 and 2008. The translation to human/clinical research of each study was evaluated by analyzing the frequency of citation in human studies over the ten years following publication. Regression was used to identify predictors of citation in human/clinical research.

Results: 411 animal studies using surgical models were identified. Over the course of the 10 years following publication the original animal studies were cited 6063 times, with 1300 (21.4%) citations in human/clinical studies and 4763 (78.6%) in animal/basic science studies. The median number of citations in human/clinical research was 1 (IQR 0–5). Regression showed an association between citation in human/clinical research and the use of porcine models and the specialties of general surgery, oral and maxillofacial surgery, orthopedic surgery, transplant, and plastic surgery.

Conclusion: The use of animal models in surgical research shows poor translation to human/clinical research. Alternative surgical models should urgently be explored.

1. Introduction

Traditionally, animals have been used as models for investigation in medicine, but the clinical relevance of knowledge gained from animal studies has been repeatedly questioned [1–3]. Animal studies often have methodological flaws that jeopardize translation to human/clinical research [2]. Methods to evaluate animal research and guidelines for the conduct and reporting of animal studies have been developed to address these concerns [2,3].

Animal models may be particularly useful to test surgical procedures before human application. Inter-species differences at the molecular or genetic level are less relevant in surgical studies due to the focus on anatomic similarities. One of the earliest and most clinically successful examples of the use of a surgical animal model was the development of the tracheostomy procedure through testing on goats by Ibn Zuhr in the 12th century [4]. Other examples that advanced the field of surgery include the experimental work on dogs in the 1900s by Georg Kelling, which set the platform for modern day laparoscopy, and by Vivien Thomas and Alfred Blalock, which pioneered the repair of Fallot's tetralogy [5,6]. However, the current surgical era focuses on the refinement and standardization of established procedures more than on the introduction of new techniques and, for ethical and scientific reasons, the role of surgical animal models requires an objective re-evaluation.

In this study, we sought to objectively evaluate the translation to human/clinical research of studies employing surgical animal models by analyzing the frequency of their citation amongst human studies over the 10 years following publication.

* Corresponding author. Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 E 68th St, New York, NY, 10065, USA.
E-mail address: mfg9004@med.cornell.edu (M. Gaudino).

[1] Equal contribution.

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2. Methods

2.1. Journal and study selection

The top two ranking clinical journals based on impact factor for the top ten surgical specialties (cardiac and thoracic surgery, general surgery, neurosurgery, obstetrics and gynecology, oral and maxillofacial surgery, orthopedic surgery, plastic surgery, transplant, urology, and vascular surgery) were identified on Google Scholar Metrics [7] and a search was run on PubMed to identify studies using surgical animal models published in the years 2007 and 2008. This returned 1631 results. The detailed search strategy is presented in the Supplementary Appendix. Three independent reviewers (B.R., I.H, and A.N.) manually screened the 1631 studies to identify surgical animal model studies and disagreements were resolved by a fourth author (M.G.). Articles were considered for inclusion if they were written in English and were conducted utilizing in-vivo surgical procedures using animal models. Studies that did not clearly describe a surgical intervention, involved animal cell and tissue cultures for basic research, in-vitro, ex-vivo, organ harvesting, and surgical maneuvers related for physiologic changes were excluded. Citations in case reports, conference presentations, editorials, letters, and expert opinions were also excluded. This work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria [8].

Each included article was searched on Web of Science to identify the total number of citations from 2007 to 2018 and the year of citation [9]. The citations were manually assessed by two reviewers (Y.R. and I.H.). They were then classified as “human/clinical” if they reported a clinical observational study or randomized controlled trial involving human patients or “animal/basic science” if they described basic science research involving animals or cell/tissue-level experiments. For each included article, the following data were recorded: the surgical animal model studied, surgical specialty, subgroup (device vs. outcome vs. technique), outcome (positive vs. negative vs. neutral), and journal of publication.

2.2. Statistical analysis

Categorical data are presented as frequency and percentages, and continuous data are presented as median and inter-quartile range (IQR) after testing for normality. Mann-Whitney *U* test was used to compare categorical and continuous data respectively among groups.

Multiple regression was performed to identify any predictors of citation in human/clinical research amongst the variables of surgical specialties and different animal models used. P-value < 0.05 was considered statistically significant. All analyses were performed using R (version 3.4.2 R Project for Statistical Computing) within RStudio.

3. Results

A total of 21,413 articles were published in the 20 chosen journals between January 2007 and December 2008 (Tables 1 and 3). Of these, 411 (1.9%) involved surgical animal models and were eligible for analysis. There were 178 (43.3%) device-related studies, 142 (34.5) outcomes studies, and 91 (22.1) surgical technique studies. Study outcomes were mostly positive (n = 343, 83.5%) Table 2. A majority of the studies utilized mouse models (212 [51.6%]), while monkey/primate models were used less frequently (9 [2.2%]). Details of the surgical animal models used are presented in Table 4.

Surgical animal model studies were cited in a total of 6063 times between 2007 and 2018. Among them, 1300 (21.4%) citations were in human/clinical studies and 4763 (78.6%) were in animal/basic science studies (Table 3). Fig. 1 summarizes the frequency of surgical animal model study citations in human/clinical and animal/basic science articles.

The median number of citations in human/clinical and animal/basic science articles was 1 (IQR 0–5) and 8 (IQR 4–17), respectively ($p < 0.001$, Fig. 2). The annual number of citations in human/clinical articles were significantly lower than in animal/basic science articles ($p < 0.001$), reaching a peak in 2011 (Fig. 3).

On multivariable analysis, studies in the fields of general surgery, oral and maxillofacial surgery, orthopedic surgery, transplant, and plastic surgery, as well as the use of a porcine model were significantly associated with citation in human/clinical research articles. Studies describing a surgical technique were significantly less likely to be cited in a subsequent human/clinical research article. (Table 5).

Table 1
Number of studies using surgical animal models from 2007 to 2008 by surgical specialty and top two highest impact journals within each specialty.

Specialty and Journal	Number of studies (%)[a]
Gynecology & Obstetrics	8 (1.9)
• *American Journal of Obstetrics & Gynecology*	7 (1.7)
• *Obstetrics & Gynecology*	1 (0.2)
Heart & Thoracic Surgery	112 (27.3)
• *Journal of Thoracic and Cardiovascular Surgery*	76 (18.5)
• *Annals of Thoracic Surgery*	36 (8.8)
Neurosurgery	19 (4.6)
• *Neurosurgery*	18 (4.4)
• *Journal of Neurosurgery*	1 (0.2)
Oral & Maxillofacial Surgery	11 (2.7)
• *Clinical Implant Dentistry and Related Research*	10 (2.4)
• *International Journal of Oral & Maxillofacial Implants*	1 (0.2)
Orthopedic Medicine & Surgery	43 (10.5)
• *Clinical Orthopaedics and Related Research*	24 (5.8)
• *The Journal of Bone & Joint Surgery*	19 (4.6)
Plastic	87 (21.2)
• *Plastic and Reconstructive Surgery*	49 (11.9)
• *Journal of Plastic, Reconstructive, & Aesthetic Surgery*	38 (9.2)
Surgery	28 (6.8)
• *Annals of Surgery*	18 (4.4)
• *British Journal of Surgery*	10 (2.4)
Transplantation	31 (7.5)
• *American Journal of Transplantation*	16 (3.9)
• *The Journal of Heart and Lung Transplantation*	15 (3.6)
Urology & Nephrology	36 (8.8)
• *The Journal of* Urology	29 (7.1)
• *European Urology*	7 (1.7)
Vascular Medicine	36 (8.8)
• *Journal of Vascular Surgery*	27 (6.6)
• *European Journal of Vascular and Endovascular Surgery*	9 (2.2)
Citation of Human clinical Research (median [IQR])	1 [0, 5]
Citation of original basic Research (median [IQR])	8 [4,17]

[a] Percentages were calculated per specialty and journal separately.

Table 2
Article outcomes and subtype.

Outcome	Number of studies (%)
• Positive	343 (83.5)
• Neutral	56 (13.6)
• Negative	12 (2.9)
Subgroup	
• Devices	178 (43.3)
• Outcomes	142 (34.5)
• Technique	91 (22.1)

4. Discussion

We found that the translation of results from surgical animal studies to human/clinical research is very limited. Out of more than 6000 citations, less than 15% were in human/clinical research studies and the median number of citations in human articles was one. Studies involving the surgical specialties of OMFS, general surgery, plastic surgery, orthopedic surgery, and transplantation were more likely to have a

Table 3
Citations of studies using surgical animal models over the course of 10 years.

Surgical Specialty	Total number of publications in the top two journals for each specialty (2007–2008)	% of publications involving SAMs	Citations (2007–2018)		
			Total number of eligible citations of SAM studies	% of citations in human/ clinical studies (n = 1300)	% of citations in animal/ basic science studies (n = 4763)
Cardiac and Thoracic Surgery	3556	3.1	1307	22.8	77.2
General Surgery	1222	2.3	826	24.7	75.3
Neurosurgery	2230	0.9	286	16.1	83.9
Obstetrics and Gynecology	2369	0.3	66	22.7	77.3
Oral and Maxillofacial Surgery	353	3.1	245	19.2	80.8
Orthopedic Surgery	2065	2.1	1239	18.6	81.4
Plastic Surgery	2973	2.9	360	14.7	85.3
Transplant	1321	2.3	706	22.1	77.9
Urology	3721	1.0	591	25.0	75.0
Vascular Surgery	1603	2.2	437	23.3	76.7
TOTAL	21,413	1.9	6063	21.4	78.6

Table 4
Frequency of surgical animal models.

Surgical animal model	Frequency in studies
Chicken/sheep/lamb/horses	48 (11.7)
Dogs	50 (12.2)
Mice	212 (51.6)
Monkeys/primates	9 (2.2)
Pigs	92 (22.4)

subsequent citation in human/clinical research. Notably, papers describing techniques were less likely to be cited.

While internal validity is a key area for improvement in animal studies, external validity due to biomolecular dissimilarities between species is the most important factor that limits translation to human research [10–13]. In surgical studies, however, animal models are chosen for similarity to gross human anatomy and molecular or genetic differences may play a more limited role [13,14].

Our results are consistent with previous data in showing very poor translation of surgical animal studies to human research [15]. We speculate that, in the modern surgical era, there is a focus on refining techniques and outcomes rather than introducing new surgical procedures, and the use of anatomic analogues is not enough to achieve results that can be translated into human research [4]. As an example,

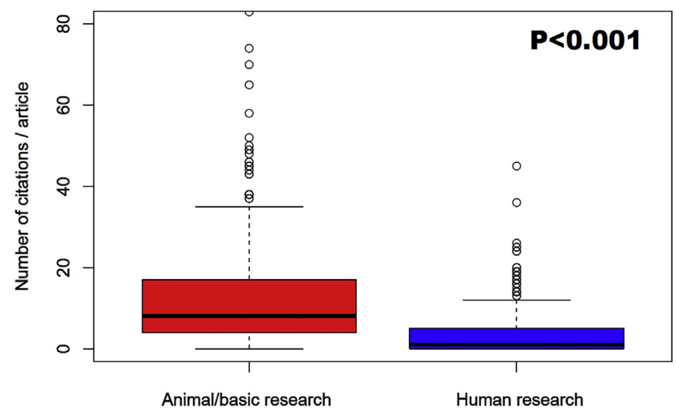

Fig. 2. Citations in animal/basic science and human/clinical articles. Interpretation: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; thick horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Circles represent outliers.

obtaining long-term follow-up or imaging data is difficult in animal models, but it is key to achieve meaningful research results in surgery [2].

Clinical translation is one of the primary justifications for the

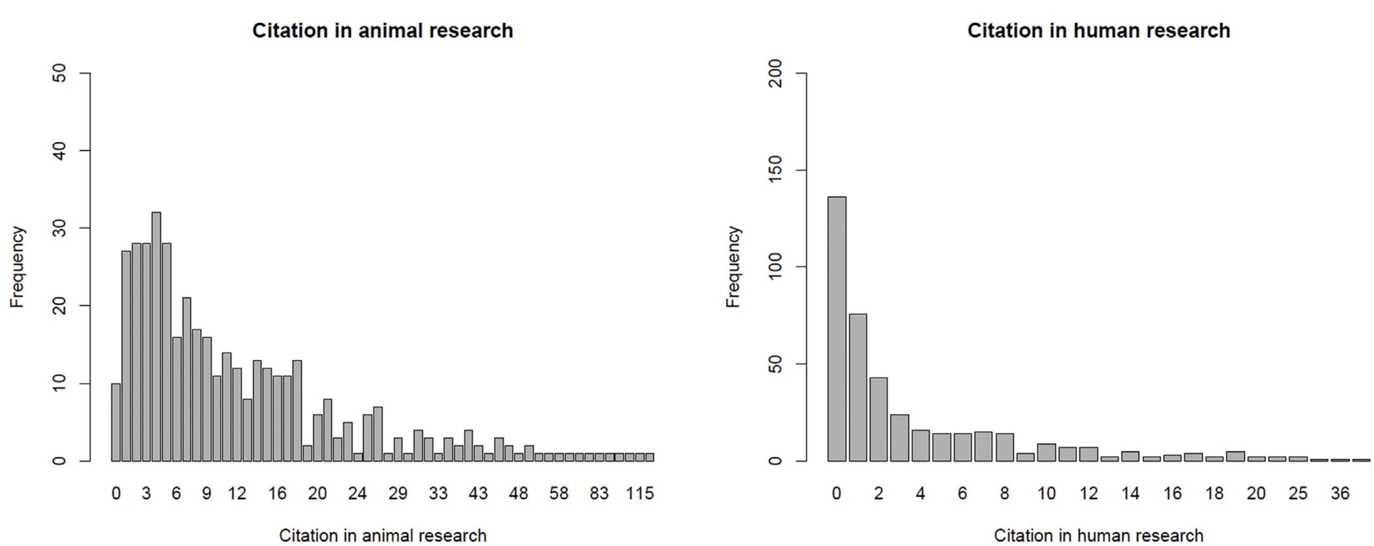

Fig. 1. Frequency of citations in animal/basic science and human/clinical articles.

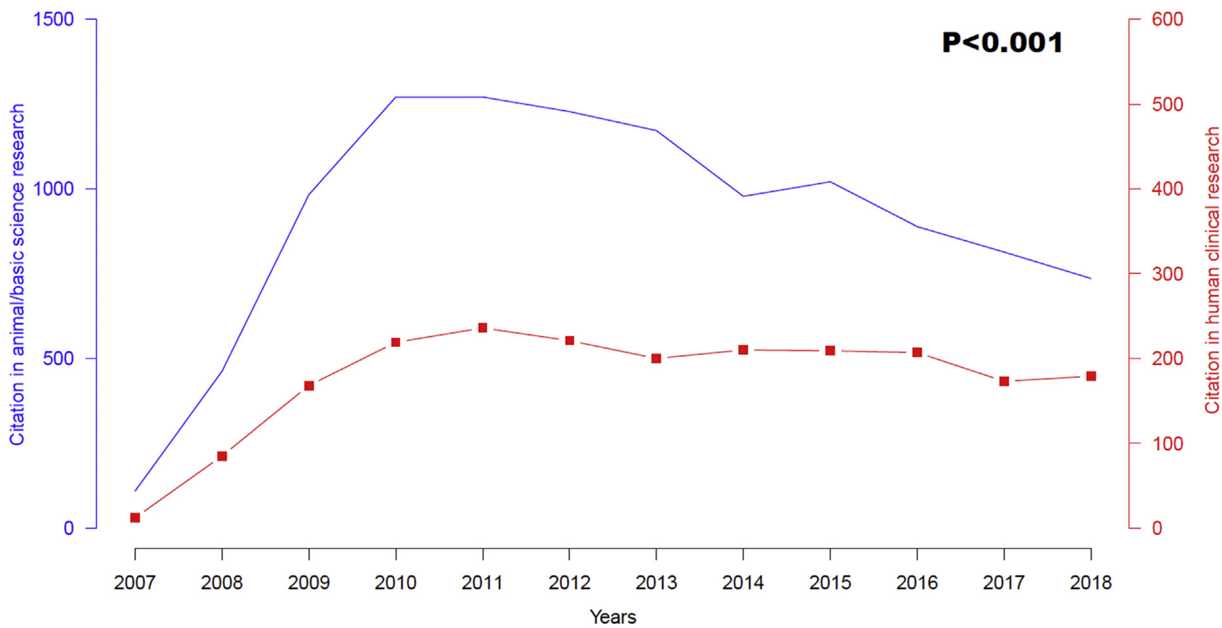

Fig. 3. Annual number of citations in animal/basic science versus human/clinical research. The annual number of citations in human/clinical studies were significantly lower than in animal/basic science studies ($p < 0.001$, Chi square test).

Table 5
Predictors of citations in human/clinical research.

Variable	Regression coefficient (beta) (95% confidence interval)
Surgical specialty (vs Cardiac and Thoracic Surgery) ¶	
• Gynecology/Obstetrics	−0.26 (−0.84, 0.32)
• Neurosurgery	−0.18 (−0.52, 0.16)
• Oral Maxillofacial Surgery	0.67*** (0.33, 1.00)
• Orthopedic Surgery	0.62*** (0.43, 0.80)
• Plastic	0.40*** (0.22, 0.58)
• Surgery	0.76*** (0.56, 0.95)
• Transplantation	0.46*** (0.25, 0.68)
• Urology Nephrology	0.25** (0.04, 0.46)
• Vascular surgery	−0.14 (−0.38, 0.10)
Surgical animal model (vs Dogs)	
• Pigs	0.47*** (0.25, 0.70)
• Chicken/sheep/lamb/horse	0.59*** (0.35, 0.82)
• Mice	0.51*** (0.29, 0.72)
• Monkeys/primates	0.52*** (0.16, 0.89)
Outcome (vs Negative)	
• Neutral	0.30 (−0.14, 0.74)
• Positive	0.25 (−0.17, 0.66)
Subgroup (vs Device)	
• Outcome	0.02 (−0.11, 0.15)
• Technique	−0.27*** (−0.42, −0.11)

¶ Cardiac and Thoracic Surgery was used as a reference as it has the highest number of included studies.
*$p < 0.1$; **$p < 0.05$; ***$p < 0.01$.

continued use of surgical animal models. The limitations in the translation of surgical animal model studies to human research, the unnecessary suffering of the animals involved, and the wasted financial resources raise questions of a moral and ethical nature. Simulation models are an alternative medium gaining popularity for surgical research and may represent a more ethical and effective approach [13].

To be sure, animal models have provided significant contributions in the advancement of medicine. Novel procedures and medications are routinely trialed on animal models in pre-clinical trials. In the modern era, however, practical and ethical concerns have led some to question the continued use of animals in research. In a recent analysis of cancer literature, for example, it was found that less than 8% of pre-clinical studies translated to human clinical trials [16]. Until better translation is noted, alternatives should be explored in the pre-clinical setting.

Several limitations of this review need to be considered. Firstly, our review did not individually evaluate surgical animal studies for methodology. This makes it difficult to accurately predict whether faulty methodology may have been one of the factors that hindered clinical translation. Additionally, we only used Web of Science to identify citations so it is possible that some citations present in other databases may have been missed. The method of using citation counts to estimate research impact itself is controversial with a known restriction of time needed for citation accruement [17]. We tried to compensate for this by reviewing studies published ten years prior. Additionally, we did not capture whether a subsequent human citation was the foundation for further studies, rendering the original animal citation more clinically important. Finally, we only analyzed studies in the top surgical journals making clinical translation more likely than studies published in less well-known journals. Unfortunately, this suggests that there are even lower rates of translation from animal research to clinically significant human advancement.

5. Conclusion

Our study provides essential insights on the usefulness of animal models in surgical research in the contemporary era and suggests that results from animal models are poorly translated into human/clinical research. Surgical model alternatives to animals should be urgently explored.

Ethical approval

Ethical approval was not required.

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Author contribution

All authors listed have made contributions to the review. NBR and MG designed the study. NBR, YR, FMK, IH, MR, AN, CTO, LR, LNG, and

MG participated in collecting the data, analysing the data, drafting the manuscript, revising the manuscript. All authors read the final manuscript and approved it.

Trial registry number

Name of the registry: Not applicable.Unique Identifying number or registration ID: Not applicable.Hyperlink to the registration (must be publicly accessible): Not applicable.

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Mario Gaudino MD, corresponding author.

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Abbreviations

None.

Data statement

The data obtained in this study can be made available upon request.

CRediT authorship contribution statement

Yongle Ruan: Writing - original draft, Data curation. **N. Bryce Robinson:** Writing - original draft, Conceptualization, Methodology, Data curation. **Faiza M. Khan:** Writing - original draft, Conceptualization, Methodology. **Irbaz Hameed:** Writing - original draft, Data curation. **Mohamed Rahouma:** Writing - original draft. **Ajita Naik:** Writing - original draft, Data curation. **Christian T. Oakley:** Writing - original draft, Data curation. **Lisa Rong:** Writing - original draft. **Leonard N. Girardi:** Writing - original draft. **Mario Gaudino:** Writing - original draft, Conceptualization, Methodology.

Declaration of competing interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2020.03.023.

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