Evaluation of neurosurgical implant infection rates and associated pathogens: evidence from 1118 postoperative infections

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OBJECTIVE Various implanted materials are used in neurosurgery; however, there remains a lack of pooled data on infection rates (IRs) and infective bacteria over past decades. The goal of this study was to investigate implant infections in neurosurgical procedures in a longitudinal retrospective study and to evaluate the IRs of neurosurgically implanted materials and the distribution of pathogenic microorganisms.

METHODS A systematic literature search was conducted using PubMed and Web of Science databases for the time period between 1968 and 2018. Neurosurgical implant infections were studied in 5 subgroups, including operations or diseases, implanted materials, bacteria, distribution by country, and time periods, which were obtained from the literature and statistically analyzed. In this meta-analysis, statistical heterogeneity across studies was tested by using p values and I² values between studies of associated pathogens. Egger's test was used for assessing symmetries of funnel plots with Stata 11.0 software. Methodological quality was assessed to judge the risk of bias according to the Cochrane Handbook.

RESULTS A total of 22,971 patients from 227 articles satisfied the study's eligibility criteria. Of these, 1118 cases of infection were reported, and the overall IR was 4.87%. In this study, the neurosurgical procedures or disorders with the top 3 IRs included craniotomy (IR 6.58%), cranioplasty (IR 5.89%), and motor movement disorders (IR 5.43%). Among 13 implanted materials, the implants with the top 3 IRs included polypropylene-polyester, titanium, and polyetheretherketone (PEEK), which were 8.11%, 8.15%, and 7.31%, respectively. Furthermore, the main causative pathogen was *Staphylococcus aureus* and the countries with the top 3 IRs were Denmark (IR 11.90%), Korea (IR 10.98%), and Mexico (IR 9.26%). Except for the low IR from 1998 to 2007, the overall implant IR after neurosurgical procedures was on the rise.

CONCLUSIONS In this study, the main pathogen in neurosurgery was *S. aureus*, which can provide a certain reference for the clinic. In addition, the IRs of polypropylene-polyester, titanium, and PEEK were higher than other materials, which means that more attention should be paid to them. In short, the total IR was high in neurosurgical implants and should be taken seriously.

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KEYWORDS neurosurgery; cranioplasty; cerebral surgery; infective bacteria; infection rate

NEUROSURGERY has many complications including bone resorption, implant exposure, wound dehiscence, delayed hydrocephalus, and infection.^{2,76} Among the various complications, infections associated with neurosurgery can be disastrous, leading to removal of bone or prosthetic flaps, extended hospital stays, and surgical revisions. In recent prospective single-center studies, infection rates (IRs) after cranial neurosurgical procedures

varied between 1.6% and 9%.^{13,15,49,82} Recent articles have reported that the overall postoperative IR from cranioplasty is comparatively high, ranging from 3.7% to 25.6%.^{94,95}

Recent studies regard the success of neurosurgery as dependent on a variety of factors, such as the size and location of neurosurgery procedures, the patient's condition, the implantation time, and the material used.^{6,37,95} The ideal implanted material has the following characteristics: en-

ABBREVIATIONS HA = hydroxyapatite; IR = infection rate; PEEK = polyetheretherketone; PMMA = polymethylmethacrylate; SSI = surgical site infection.

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hances aesthetic appearance, is easily affixed to the skull, has low heat conduction, has strong biomechanical processes, and is lightweight, easily shaped, chemically inert, sterilizable, osteoconductive, biocompatible, inexpensive, and readily available.^{59,71} However, the choice of material for neurosurgical practice is still controversial,^{47,78,90} because every material has its own unique set of merits and demerits.

At present, various materials have been used successfully for cranial reconstruction; these include autogenous bone grafts and xenogeneic or alloplastic implants.^{50,84} For example, autologous bone is not subject to immune rejection and is effective as a substrate for bone ingrowth and revascularization.^{14,53} However, there is a risk of resorption, graft infection, longer hospitalization periods, insufficient autogenous grafts, and difficulty in contouring the bone to fit the defects.^{16,31,73,79,90,94} In order to circumvent these problems that exist for autologous bone, several synthetic materials are available for reconstructive surgery. At present, there are primarily 3 types of allografts: metal, ceramic, and polymer.¹⁰ Titanium as a bone substitute biomaterial is valued for its stability and biocompatibility with a low IR.⁵⁵ However, titanium also has disadvantages—for example, the material is expensive and has a lack of reintegration into the surrounding bone.^{35,92} Hydroxyapatite (HA) is a ceramic material that has gained popularity in recent years because of its osteoconductive, non-thermal-conducting features and excellent aesthetic results.^{8,38,80} Unfortunately, HA may be at risk for failure due to risk of hematoma, seroma, infections, and implant exposure.^{8,80} Since the 1940s, polymethylmethacrylate (PMMA), a polymer, has remained the most widely used material because of its low cost, radiolucency, and stability, and because it is easily moldable and biologically inert.⁷ Nonetheless, its use does come with drawbacks such as infection, fragmentation, and a lack of incorporation.^{14,35}

The aim of this meta-analysis was to analyze neurosurgical implant infections and causative bacteria over the past decades. Despite the profusion of reports from different parts of the world regarding implanted materials in neurosurgery, there remains a lack of pooled data on IRs and infective bacteria over the past decades. Herein we have systematically reviewed the literature for all reported data on neurosurgical procedures and other operations associated with infection, implanted materials, infective bacteria, countries in which cases were treated, and time periods.

Methods

Search Strategy

Two independent reviewers (L.Z. and T.Q.) conducted a systematic literature review of potentially qualifying articles and relevant medical journals that reported neurosurgical procedures associated with implant infections. A comprehensive search of the scientific literature was undertaken by querying the electronic databases of PubMed and Web of Science up to April 2018 by using the National Library of Medicine's MeSH terms "neurosurgery" or "cerebral surgery" or "cranioplasty" and "implant infections." The search was not restricted by language, pub-

lication status, or geographical distribution of the publications.³³ If an article was related, then the full text would also be retrieved. When necessary, additional contact was made with the authors of the included articles to ascertain data.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were defined by the researchers prior to the review of literature. The purpose of the search was to discover articles that met the following inclusion criteria: 1) case series reporting the outcome in at least 5 patients; 2) publication date before April 2018; and 3) the data regarding implant infections were clear. Exclusion criteria applied to studies were as follows: 1) articles irrelevant to humans; 2) review, case report, or meta-analysis; 3) implanted materials not mentioned and operations irrelevant to neurosurgery; and 4) data unclear and articles duplicative. Furthermore, technical notes, letters, and editorials were excluded.

Validity Assessment

A systematic review was performed in accordance with PRISMA guidelines. Two separate individuals (L.Z. and T.Q.) independently performed study selection and quality assessment using the Cochrane Handbook, version 5.1.0 (<http://handbook-5-1.cochrane.org>). The evaluation criteria of each item were judged as "low risk of bias," "unclear risk of bias," and "high risk of bias." If there was any question about the eligibility of an article, data discrepancies were determined through reevaluation by a senior author (B.G.), who could set aside the outcome of the preceding assessment.²⁸

Data Extraction and Analysis

The data extracted from each article included the following: number of patients, operations, and diseases; number of implant materials and infections; IRs; infective bacteria; patient ages; study period; treatment; study subject; country; follow-up; first author; and year of publication. Divergences among any of the above data points were resolved through discussions among the authors. Subgroup analysis was performed to determine the IRs after neurosurgical procedures.

We evaluated the heterogeneity with I^2 values according to the Cochrane Handbook.⁵⁷ The fixed-effects model was applied for data synthesis of low heterogeneity ($I^2 < 50\%$), whereas the random-effects model was conducted if the heterogeneity was significant ($I^2 \geq 50\%$). If heterogeneity was evaluated as significant ($I^2 \geq 50\%$) and the trials included were adequate, we performed a subgroup analysis to explore the potential source of the heterogeneity.

Egger's test was used to assess symmetries of the funnel plot with the aid of Stata 11.0 software. The presence of reporting bias was evaluated by Egger's test when studies included in the review were sufficient (> 10 trials). The intercept of the regression line represents the degree of asymmetry deviation. Reporting bias was considered to exist and reliability was considered to be low when the intercept on Egger's graph was far from zero. Conversely, when the intercept on Egger's graph was close to zero, the

FIG. 1. Flow diagram for selection of studies.

reporting bias was considered to be nonexistent and the result to be reliable.

Results

Systematic Literature Search

A total of 1387 articles were identified with the original electronic database search (Fig. 1). A further 43 articles were also identified through manual search, bibliographic search, and reviewer suggestions. After excluding duplicate studies and articles not directly related to our hypothesis, a total of 933 articles remained. Finally, 227 full-text articles were subsequently analyzed based on the inclusion and exclusion criteria established for the review. Systematic review and meta-analysis were performed for 227 studies with a total of 22,971 patients, 1118 cases of infection were reported, and the total IR was 4.87%.

Assessment of Publication Bias

As can be seen from Egger's publication bias plot (Fig. 2), the intercept of the regression line is close to zero, there is no obvious visual bias, and the result is reliable. In this review, for estimation of publication bias, no statistically significant asymmetry was found according to Egger's test ($t = -1.60$, $p > 0.05$), which means that no significant publication bias was found among studies.

IRs of Operations

In this study, 9 primarily neurosurgical operations or diseases were counted; some operations were not counted if the number of patients was less than 100. Therefore, a total of 17,632 patients were included, 854 cases of infection were reported, and the overall IR was 4.84% (Table 1). The most common neurosurgical procedures were cranioplasty, motor movement disorders, and craniostomy—among these, 8273 patients underwent cranioplasty. As can be seen from Table 1, the procedures with the top 3 IRs were operations including craniotomy (IR 6.58%), cranioplasty (IR 5.89%), and motor movement disorders (IR 5.43%). In our statistics, motor movement disorders included tremor, spasticity, dystonia, and Parkinson disease; the IR for these disorders was second only to the IRs for cranioplasty and craniotomy, and in recent years these surgeries have also received attention. However, the lower IRs included duraplasty, hydrocephalus, and craniostomy, which were 3.17%, 2.59%, 0.77%, respectively.

FIG. 2. Egger's publication bias plot of neurosurgical implant infection.

TABLE 1. IRs of the 9 most common neurosurgical procedures

Operation	Total	No. of Infections	IR (%)
Craniotomy	1033	68	6.58
Cranioplasty	8273	487	5.89
Motor movement disorders	3278	178	5.43
Spinal/brain metastases	158	7	4.43
Craniofacial surgery	707	30	4.24
Epilepsy	1185	47	3.97
Duraplasty	315	10	3.17
Hydrocephalus	348	9	2.59
Craniosynostosis	2335	18	0.77
Total	17,632	854	4.84

TABLE 2. IRs of the 13 most common implanted materials

Material	Total	No. of Infections	IR (%)
Implanted pump	1466	138	9.41
Titanium implants	810	66	8.15
Polypropylene-polyester	296	24	8.11
PEEK	520	38	7.31
Deep brain stimulation electrodes	1755	115	6.55
Autologous bone	973	64	6.58
Gliadel wafers	454	26	5.73
PMMA	1223	70	5.72
Pulse generator	273	11	4.03
HA	694	21	3.03
Medpor porous polyethylene	818	8	0.98
Biodegradable or resorbable devices	2897	26	0.90
Dura mater	172	1	0.58
Total	12,351	608	4.92

IRs of Implanted Materials

We did a statistical analysis of 13 implanted materials in this meta-analysis, comprising titanium, polypropylene-polyester, PMMA, polyetheretherketone (PEEK), Medpor porous polyethylene, HA, autologous bone, dura mater, Gliadel wafers, deep brain stimulation electrodes, implanted pumps, pulse generators, and biodegradable/resorbable devices. A total of 12,351 patients were selected, 608 cases of infection were reported, and the overall IR was 4.92% (Table 2). Of the 13 implanted materials, the IRs of Medpor porous polyethylene, biodegradable or resorbable devices, and dura mater were lowest; these were 0.98%, 0.90%, and 0.58%, respectively. The highest 3 IRs were observed with polypropylene-polyester (IR 8.11%), titanium implants (IR 8.15%), and PEEK (IR 7.31%).

Distribution of Pathogenic Microorganisms

In this meta-analysis, a total of 14 bacterial genera plus anaerobic species were selected, and 34 studies covering

TABLE 3. Distribution of pathogenic microorganisms associated with neurosurgical procedures in 34 studies

Bacteria	Total	%
<i>Staphylococcus</i> spp.	282	76.22
<i>S. aureus</i>	198	53.51
Coagulase-negative <i>Staphylococcus</i>	74	20.00
Unidentified	10	2.70
<i>Streptococcus</i> spp.	7	1.89
α-hemolytic streptococci	1	0.27
β-hemolytic streptococci	4	1.08
Nonhemolytic group D streptococci	1	0.27
Unidentified	1	0.27
<i>Propionibacterium</i> spp.	27	7.30
<i>P. acnes</i>	20	5.41
Unidentified	7	1.89
<i>Klebsiella</i> spp.	7	1.89
<i>K. pneumoniae</i>	3	0.81
<i>K. oxytoca</i>	3	0.81
Unidentified	1	0.27
<i>Escherichia coli</i>	8	2.16
<i>Enterobacter</i> spp.	14	3.78
<i>E. aerogenes</i>	1	0.27
<i>E. cloacae</i>	4	1.08
<i>E. aeruginosa</i>	6	1.62
Unidentified	3	0.81
<i>Serratia marcescens</i>	3	0.81
<i>Proteus mirabilis</i>	3	0.81
<i>Providentia stuartii</i>	1	0.27
<i>Morganella morganii</i>	1	0.27
<i>Pseudomonas</i> spp.	7	1.89
<i>P. aeruginosa</i>	5	1.35
Unidentified	2	0.54
<i>Acinetobacter baumannii</i>	1	0.27
Anaerobic spp.	3	0.81
<i>Candida</i> spp.	6	1.62
<i>C. albicans</i>	1	0.27
<i>C. famata</i>	1	0.27
<i>C. parapsilosis</i>	1	0.27
Unidentified	3	0.81
Total	370	100

370 bacterial infection cases were contained in our selected literature (Table 3). The 34 studies describing neurosurgery gave a bacterial distribution estimate of 0.05 (95% CI 0.04–0.07). Statistically significant heterogeneity was observed between studies ($p < 0.001$, I^2 83.9%) (Fig. 3). In our study population, the predominant pathogenic microorganism isolated was *Staphylococcus aureus* (53.51%), which is consistent with other reports,^{30,43,61,67,72,77} followed by coagulase-negative *Staphylococcus* (20.00%) and *Propionibacterium acnes* (5.41%). Therefore, the regimen selected should be aimed at these pathogenic microorganisms.

FIG. 3. Forest plot for the meta-analysis of the IR of associated bacteria of neurosurgery (meta-analysis using the random-effects model). The D + L value is the weight that different studies contribute to the combined accuracy ratio. The higher I^2 values combined with p values > 0.01 denote greater heterogeneity between those studies. ES = error standard (i.e., standard error).

Distribution of IRs by Country

Among 227 studies, only 3 articles reported cases by continent;^{9,22,26} therefore, 857 patients were not included. We have calculated that in 22,114 patients from a total of 32 countries in 224 studies, 1050 cases of infection were reported, and the overall IR was 4.75%. Notably, the IRs in Denmark, Korea, and Mexico were high (Fig. 4), which should encourage surgeons in those countries to pay more attention to preventing infections from implants. In China, a total of 540 patients were selected from 16 articles, 26 infections were counted, and the overall IR was 4.81%, which is slightly above the total IR. In addition, a total of 10,869 cases were included from the US in 82 articles, 446 infections were reported, and the overall IR was 4.10%, which is less than the total IR for all studies.

IRs of Time Periods

The time period was equally divided into 5 time slots,

including 1968–1977, 1978–1987, 1988–1997, 1998–2007, and 2008–2018, but because only 1 article was reported in 1968, we only listed 4 time slots. As seen in Table 4, the IR from 2008 to 2018 increased yearly. In the past decades, except for the low IR from 1998 to 2007, the overall implant IRs after neurosurgical procedures have been on the rise, which can provide a certain reference for the clinic.

Discussion

The development of implant infections in neurosurgery is a significant complication and often requires reoperation, an extended hospital stay, and therapy with antibiotics. To date, cranioplasty is the most common procedure associated with implantation; it can restore cosmesis, provide cerebral protection, facilitate neurological rehabilitation, improve neurological outcome^{36,40,62} and provide protection to the underlying brain, and normalize cerebral hemodynamics and metabolism.^{28,42,52,83} Because of these

FIG. 4. Map of the distribution of IRs by country.

advantages, cranioplasty has recently become more common in neurosurgical practice. The IR of cranioplasty will hopefully decrease as surgeons' experience and awareness of infection prevention and control gradually increase.

The IRs of implants and equipment, however, are still high in the application of these neurosurgical procedures. In addition, infection remains a core concern with regard to implant failure and patient health.^{39,68} There are many causative factors that can impact the infection risk for a patient, such as preexisting infections, the latency period between tissue removal and implant insertion,^{39,46} and operating time.^{68,85} Neurosurgical implants include fixation devices for craniotomy, synthetic cranioplasties, various polymers, metal or ceramic materials, internal shunt systems, external ventricular drains, and neurostimulators.⁵¹ When comparing the IRs of different implants, it is essential to recognize differences such as material properties, biocompatibility, and bioactivity. Autologous bone is not subject to immune rejection and is effective as a substrate for bone ingrowth and revascularization.^{7,38} Khan et al. stated that the IRs of autologous bone varied between

5.93% and 25%, with an average IR of 10.50%,⁴⁵ which was in line with our studies (IR 6.58%). Lee et al. reported that autologous implants had significantly more reoperations than synthetic implants,⁵⁴ which could impact the effectiveness of potential vascularization and reintegration,^{31,91} resulting in the autologous bone being shielded from the immune system and therefore presenting an ideal scaffold for bacteria, as well as a risk of implant failure, donor-site morbidity, increased operating time, insufficient autogenous grafts, and difficulty in contouring the bone to fit the defects.^{16,73,90,91,94} However, Yadla et al. conducted a systematic review of 14 retrospective studies published between 1966 and 2010 and found no difference in IRs of autograft and allograft materials.⁹⁴

Titanium is a versatile metal and is used in a number of different structural forms in the field of cranioplasty. Forms of titanium used in neurosurgical procedures can be further split into titanium mesh and titanium plates.⁵¹ Titanium implants often require prefabrication,^{18,25} leading to an increased lead time and cost, and intraoperative alteration remains difficult.⁴ In this study, the number of titanium implants was 810, with an average IR of 8.15%, which should cause the clinician to be cautious with their use.

Resorbable bone implant systems were developed in the 1990s and have gained wide use in pediatric cranial and facial surgery.^{3,23} The absorbable plating systems do not erode bone when placed in children.¹⁹ Commercially resorbable plating systems are composed of polyglycolic and polylactic acids, and are fabricated into various plates, meshes, buttons, screws, tacks, or pins.²³ In the past few decades, resorbable materials have been the most common neurosurgical procedures, with 2897 patients included in this meta-analysis, but only 26 cases of infection were re-

TABLE 4. IRs categorized by time periods

Years	Total	Infection	IR (%)
1978–1987	1025	39	3.80
1988–1997	3108	127	4.09
1998–2007	6420	236	3.68
2008–2018	12,413	714	5.75
Total	22,966	1116	4.86

Because only 1 article from the period 1968–1977 met the criteria, it was not included in the table.

ported and the overall IR was 0.90%; this outcome was consistent with the earlier reviews.^{3,29,74} Hence, we should take these implants into account in pediatric cranial and facial surgery, considering IRs in combination with the advantages of these implants.

This study was designed to provide the highest-quality data available to detail common pathogenic microorganisms of neurosurgical practice in the past decades. According to our inclusion criteria, all bacteriological cultures should be performed using standard laboratory procedures. The main causative pathogen is *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA), which is consistent with other published reports.^{2,30,43,61,67,72,77} Given the frequency of *S. aureus* infections and their severity, the regimen selected should be aimed at these pathogenic microorganisms. Furthermore, operative technique also plays an important role in preventing postoperative infections.²⁷ Also, timing seems to be significant in avoiding complications in the neurological outcome of patients.⁹⁴ To reduce the risk of infections as complications, it is generally recommended that patients wait at least 3 months after the injury before repair of a bony deficit is attempted.⁵⁸ If the conservative treatment does not promptly improve the clinical condition of a patient, a deep incisional infection should be considered and removal of the biomaterial followed by long-term antibiotic therapy is suggested.² To our knowledge, vancomycin used in perioperative prophylaxis significantly reduces the risk of *S. aureus* surgical site infections (SSIs). Abode-Iyamah et al. assessed the use of intrawound vancomycin powder after cranioplasty and whether it would reduce the number of SSIs caused by common skin flora—theirs was the first study to evaluate the efficacy of intrawound vancomycin powder for preventing SSI after cranioplasty.² Their study did not find that intrawound vancomycin powder reduced the SSI rate. In contrast, Abdullah et al. reported that the IR among patients who did not receive vancomycin powder during craniotomy procedures was significantly higher (6.7%) than that for patients who did receive vancomycin powder (1.3%).¹ Most studies found that this practice was associated with decreased SSI rates after spine operations.^{54,69,86,88} Thus, sufficient data should be investigated in future studies and effective methods can be identified for decreasing the risk of SSI after cranioplasty.

Many studies still lack pooled data on the IRs from all over the world and their changes over a period of multiple decades. In our subgroup analysis, the IR in the US was less than the total worldwide IR. This may be related to the fact that the US is a developed country that has a sound healthcare system and a more mature technique regarding neurosurgery. In China, the overall IR is slightly above the total worldwide IR. These studies were mainly published in Taiwan, Guangdong, and Beijing—therefore, these data can only be used as a reference; the actual IR may be higher than our statistical data, and this phenomenon may be influenced by the antibiotic resistance of bacteria in China.

In this study, we found that except for the low IR from 1998 to 2007, the overall implant IRs after neurosurgical procedures were on the rise. We reanalyzed the literature published between 1998 and 2007 and found that of the 49

studies, only 14 articles from Asia and Africa were selected, among which 7 articles were published by researchers in Japan, 3 in India, and 1 in China. However, from 2008 to 2018, a total of 118 papers were counted, 30 of which were published in Asia and Africa, among which 14 articles were published by researchers in China. It can be seen that the IR of Asian and African countries was low from 1998 to 2007 due to the limited articles related to implant infection after neurosurgical procedures. However, due to the large number of articles published from 2008 to 2018, the implant IR after neurosurgical procedures had a certain referential meaning.

Our meta-analysis had some limitations. First, one limitation of our analysis is that some patients were not contacted personally after hospitalization or finally died of other nonneurosurgical diseases, so some infections may have been missed. However, the type and proportion of infections are roughly the same as the statistical results. Second, available studies consisted of published data—unpublished data were not identified. This suggests that publication bias cannot be absolutely excluded even though no significant publication bias was observed.⁵¹ It was impossible to completely exclude the influence of confounding factors inherent in these included studies, although subgroup analyses by population, sex, region, periods of time, and study design were performed. Third, the other limitation is that our analysis was based on data obtained from retrospective articles, which possibly makes it difficult to avoid and assess bias.

Conclusions

In this meta-analysis of 227 studies with 1118 patients who experienced infections, the total IR was 4.87%, which was more severe in neurosurgical procedures. The IRs of polypropylene-polyester, titanium, and PEEK implants were higher, which means that more attention should be paid to these materials. However, the IRs of Medpor porous polyethylene, biodegradable or resorbable devices, and dura mater were lower than 1.00%, so surgeons could also think about using these implanted materials in appropriate neurosurgical procedures. In addition, the most common organisms involved in implant infections after neurosurgical procedures were gram-positive organisms, such as *S. aureus*, coagulase-negative *Staphylococcus*, and *P. acnes*, which can provide a certain reference for the clinic.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Gu. Acquisition of data: Zhang, Qin. Analysis and interpretation of data: Zhang. Drafting the article: Zhang. Critically revising the article: Chen. Reviewed submitted version of manuscript: Gu. Statistical analysis: Qin, Wang, Li. Administrative/technical/material support: Chen. Study supervision: Gu, Wang, Li.

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