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REVIEW ARTICLE

Impact of postoperative NSAIDs administration on anastomotic leak after esophago-gastric surgery: systematic review and meta-analysis

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Abstract

Anastomotic leak (AL) is a feared complication of esophago-gastric surgery. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat postoperative pain. Previous analyses conveyed heterogeneous data for colorectal surgery with a tendency toward high risk for AL after NSAIDs administration. In the setting of upper gastrointestinal (GI) surgery data are even more puzzled. The purpose of the present study was to assess whether an association exists between postoperative NSAIDs administration and AL after esophago-gastric surgery. PubMed, MEDLINE, Scopus, and Web of Science were searched up to November 2022. The included studies evaluated outcomes for NSAIDs vs. no NSAIDs administration after esophago-gastric surgery. The primary outcome was anastomotic leak (AL). Risk ratio (RR) and 95% confidence intervals (95% CI) were used to assess pooled effect size and relative inference. Six studies (43,784 patients) were included. The patient age ranged from 31 to 84 years, 82.4% were males and preoperative BMI ranged from 15 to 31 kg/m^2. Esophagectomy was performed in 95% of patients. NSAIDs were administered in 18,075 (41.3%) patients. The cumulative incidence of AL was similar for NSAIDs vs. no NSAIDs (13.6% vs. 13.4%). The risk for postoperative AL was similar for NSAIDs vs. no NSAIDs administration (RR 1.49; 95% CI 0.81–2.75; $p = 0.19$). The cumulative incidence of postoperative gastrointestinal bleeding (0.36% vs. 0.39%), acute kidney injury (0.62% vs. 0.71%), and in-hospital mortality (2.39% vs. 2.66%) were comparable. NSAIDs administration for postoperative analgesia seems not associated with an increased risk for AL after esophago-gastric surgery.

Keywords Non-steroidal · NSAIDs · Esophagectomy · Gastrectomy · Anastomotic leak

Introduction

Anastomotic leak (AL) is a feared complication of esophago-gastric surgery with a wide range of reported incidence from 0 to 30% [1–3]. AL is associated with prolonged hospital stay, increased reoperation risk, reduced quality of life, increased hazard for anastomotic stricture, augmented costs, risk for 90-day mortality, and reduced overall survival [4–7]. Different risk factors for AL have been described while its prevention is of paramount importance [8–10].

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used to treat postoperative pain. With the development of intravenous formulations, use of NSAIDs in the early postoperative period has significantly augmented [11]. Furthermore, NSAIDs play a foremost role as a key opioid-sparing element of multimodal analgesia in enhanced recovery after surgery (ERAS) protocols [12–16]. However, some surgeons dissent with the use of NSAIDs in the early postoperative period since few reports suggested a potential association with AL. Specifically, previous analyses conveyed heterogeneous data for colorectal surgery with a tendency toward higher risk for leak after elective resections [17]. In the setting of upper gastrointestinal (GI) surgery, data are even more sparse while a robust indication on the potential correlation between NSAIDs and AL is unclear.

Hence, the purpose of this study was to perform a systematic review and meta-analysis to determine whether an

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association exists between postoperative NSAIDs administration and AL in the setting of upper GI surgery for esophageal and gastric anastomoses.

Materials and methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [18, 19]. The Institutional Review Board approval was not required. PubMed, MEDLINE, Scopus, Web of Science, Cochrane Central Library, and ClinicalTrials.gov were queried [20]. We searched articles from January 1st 2000 November 30th 2022. A combination of the following MeSH (Medical Subject Headings) terms was used for the literature search ("leak" (tiab), OR "anastomotic leak" (tiab) AND ("NSAIDs" (tiab), OR "non-steroidal" (tiab), OR "ketorolac" (tiab), OR "diclofenac" (tiab), OR "non-steroidal" (tiab)). AA and GB evaluated the title of each study, and suitable abstracts were extracted. The search was completed by consulting the references of each article. The study protocol was registered at the International prospective register of systematic reviews (PROSPERO registration number: CRD42022328749).

Eligibility criteria

The inclusion criteria were (a) cohort studies and randomized controlled trials (RCTs) comparing outcomes for postoperative NSAIDs versus no NSAIDs administration in adult patients (> 18 years) undergoing elective upper GI surgery (esophagectomy or gastrectomy), (b) reported in English, (c) when two or more studies were published using the same dataset, we included the study with the longest follow-up period or the largest sample size, (d) for duplicate studies, we only included the study with the complete dataset for quantitative analysis. The exclusion criteria were (a) non-English articles, (b) no clear outcome distinction between NSAIDs versus no NSAIDs administration, (c) studies including less than 10 patients for each treatment arm.

Data extraction

The following variables were collected: authors, year of publication, country, study design, number of patients, age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI), American Society of Anesthesiologists (ASA) physical status, comorbid conditions, surgical indications, tumor characteristics, histological type, tumor location, cancer stage, use of neoadjuvant chemoradiation therapy, surgical approach (open vs. minimally invasive), NSAIDs formulation, starting time from the index procedure, daily dosage (mg/day), route of administration (oral vs. intravenous), and postoperative outcomes. All data were computed independently by three investigators (AA, MM, JG) and compared at the end of the review process. Another author (DB) reviewed the database and evaluated for discrepancies.

Outcomes and definitions

The primary outcome was AL. Secondary outcomes were gastrointestinal bleeding (GIB), acute kidney injury (AKI), and in-hospital mortality. AL was defined as radiographic evidence of contrast extravasation on postoperative swallow study and/or computed tomography, or endoscopic visualization of anastomotic dehiscence/fistula, or surgical drain output consistent with saliva. GIB was defined as any bleeding from the gastrointestinal tract requiring endoscopic hemostasis or surgical reintervention. AKI was defined in accordance with the Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcomes) criteria [21].

Quality assessment

Three authors (AA, MM, GG) independently assessed the quality of methodology for each study. The ROBINS-I tool was used for observational studies [22]. The following domains were considered: confounding bias, selection bias, classification bias, intervention bias, missing data bias, outcomes measurement bias, and reporting bias. Each domain was evaluated and categorized into one of the following: "yes", "probably yes", "probably no", or "no". The categories of judgement for each study were low, moderate, serious, and critical risk of bias. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool to assess the quality of the body of evidence across studies [23].

Statistical analysis

The results of the systematic review were quantified into Frequentist random effect meta-analysis of pooled Risk Ratio (RR). An inverse-variance method and DerSimonian–Laird estimator for the variance of the true effect size (τ^2) were performed [24, 25]. Heterogeneity among studies was evaluated by the I^2 index and Cochran's Q test [26]. Statistical heterogeneity was considered low, moderate, and high for I^2 values of 25, 50, and 75%, respectively, and significant when $p < 0.10$ [27, 28]. The Wald-type 95% confidence interval (CI) was computed for pooled measurements; otherwise, the 95% CI for the I^2 index was calculated according to Higgins and Thompson [29]. The prediction interval for the treatment effect of a new study was calculated according to Borestein

[26, 30]. As the sample size was not the same in all studies, we performed a sensitivity analysis by excluding one study each time and rerunning the analysis to verify the robustness of the overall results. The publication bias was also investigated with the Trim and Fill funnel plot and Egger test. A two-sided p value was considered statistically significant when < 0.05. All analyses were performed using the R software program, version 3.2.2 [31].

Results

Systematic review

The PRISMA flow chart is reported in Fig. 1. A total of 198 publications were identified. After duplicates were excluded, 171 titles were screened, and abstracts were reviewed. After full text evaluation of 7 articles, 6 studies met the inclusion/exclusion criteria and were comprised in the quantitative synthesis. All studies were of observational design. Propensity score matching and stabilized inverse probability of treatment weighting (IPTW) were used in three studies. Four studies reported data focused on esophageal surgery, one study was focused on gastric surgery while one study reported mixed results for esophageal and gastric surgery. The quality of each study is depicted in Supplementary Table 1.

Overall, 43,784 patients were included (Table 1). The patient age ranged from 31 to 84 years and the majority (82.4%) were males. Preoperative BMI was specified in four studies and ranged from 15 to 31 kg/m^2. Patients' comorbidities were reported according to the CCI (3 studies) [32, 33, 36] and the ASA score (2 studies) [32, 33]. Tumor histology was specified in 3 studies [32, 34, 37] while the pathological stage was not informed in any of the included studies. Open, hybrid, and totally minimally Ivor-Lewis or McKeown esophagectomy were described in 95% of patients according to tumor location, operating surgeon preferences and oncologic principles. Open or minimally invasive approaches were reported for total or subtotal gastrectomy in 5% of patients. The use of neoadjuvant therapy with different protocols was reported in three studies [33, 34, 36]. The extent of lymphadenectomy was reported in four studies [32, 33, 36, 37] and varied depending on surgeon expertise, tumor clinical stage, and location. NSAIDs were administered in 18,075 (41.3%) patients in the postoperative period. Different formulations, type (selective vs. non-selective cyclooxygenase inhibitors), daily dose (mg/day)

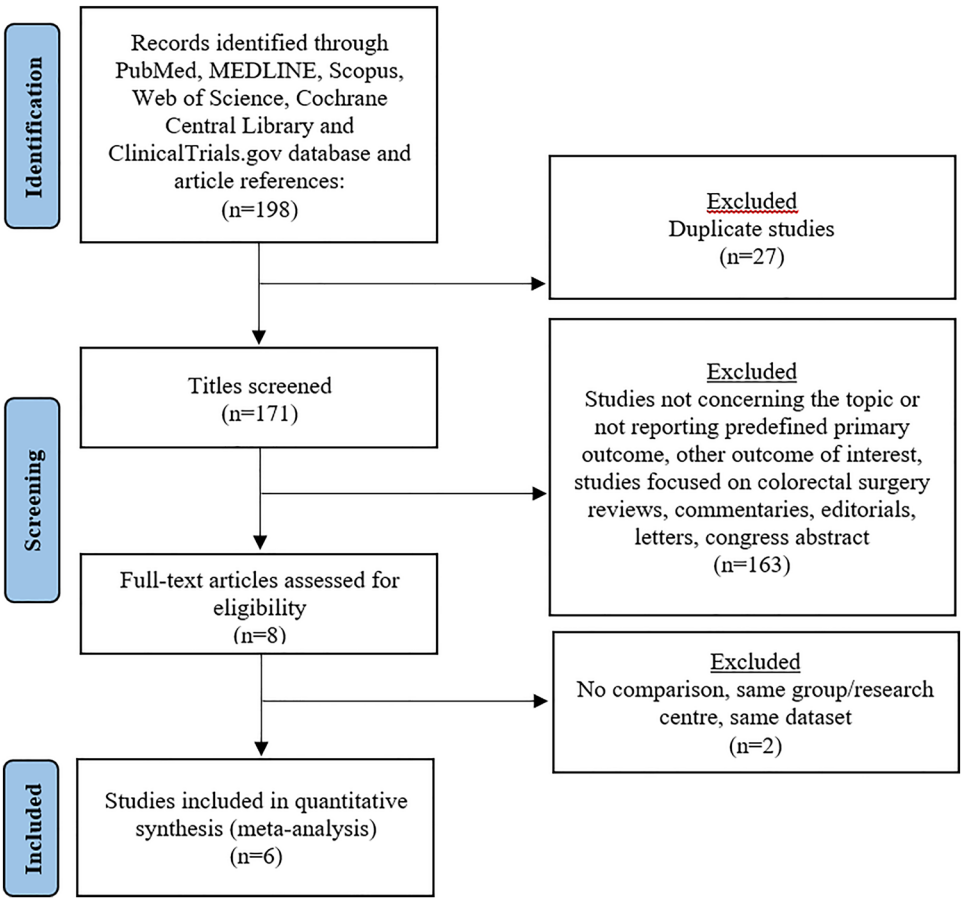

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) DIAGRAM

Table 1 1 Demographic, clinical, and operative data for NSAIDs vs. no NSAIDs postoperative administration

Author	Country	Study Design	Group	No. Pts	District	NSAIDs formulation	Age (yrs)	BMI (kg/m2)	Histology	Neoadjuvant	Surgical approach	Lymph	Cervical anastomosis	Thoracic anastomosis
Fjederhol et al. [32]	Denmark	Ret	no NSAIDs	458	Esophagus	Ketorolac, other NSAIDs	63.2	nr	ADK	nr	Open IL	2FL	0	458
			NSAIDs	98			64.5	nr		nr			0	98
Kawakami et al. [33]	Japan	Ret, IPTW	no NSAIDs	77	Esophagus	Loxoprofen, flurbiprofen	68 (42–84)	21.7 (15–31)	nr	60	Open, Hyb, MI	3FL & 2FL	77	0
			NSAIDs	73			65 (31–81)	21.7 (15–29)		68			73	0
Corsini et al., [34]	US	Ret	no NSAIDs	333	Esophagus	Ketorolac	62 (55–69)	28.3 (25–31)	ADK	861	Open, Hyb, MI	nr	nr	nr
			NSAIDs	686										
STARSurg Collaborative [35]	Europe, multi	Pros, PS	no NSAIDs	419	Esophagus Stomach	Diclofenac, ibuprofen, naproxen, celecoxib	nr	nr	nr	nr	Open, MI	nr	nr	nr
			NSAIDs	72										
Hirano et al. [36]	Japan	Ret, IPTW	no NSAIDs	23,207	Esophagus	Flurbiprofen, other NSAIDs	≥75: 2632	≥27.5: 782	nr	12,817	Open, MI	3FL & 2FL	18,716	4491
			NSAIDs	16,211			≥75: 4800	≥27.5: 610		8271			12,677	3544
Kim et al. [37]	Korea	Ret	no NSAIDs	1215	Stomach	Ketorolac	63 ± 12	23.8 ± 3.2	D: 525—U: 690	nr	LTG: 123 LSTG: 1092	D1 + 541 D2 674	/	/
			NSAIDs	935			56 ± 11	23.8 ± 3.3	D:398—U: 537	nr	LTG: 90 LSTG: 845	D1 + 523 D2 412		

Data are reported as numbers, mean ± standard deviation, and median (range)

Ret, retrospective; *IPTW*, Inverse probability of treatment weighting; *Pros*, prospective; *PS* Propensity score matching; *yrs*, years; *BMI*, body mass index; *ADK*, adenocarcinoma; *D* differentiated; *U* undifferentiated; *Hyb*, hybrid esophagectomy; *MI*, minimally invasive, *LTG*, laparoscopic total gastrectomy, *LSTG*, laparoscopic subtotal gastrectomy; *2FL*, 2-field lymphadenectomy; *3FL*, 3-field lymphadenectomy, *Nr*, not reported

and route of administration (intravenous vs. oral) were used across included studies depending of hospital availability and clinician preference. No differences were found for the comparison NSAIDs vs. no NSAIDs in term of postoperative GIB (0.36% vs. 0.39%), AKI (0.62% vs. 0.71%), and in-hospital mortality (2.39% vs. 2.66%) cumulative incidence.

Meta-analysis—anastomotic leak

AL was reported in six studies (43,784 patients). The cumulative incidence of AL was similar for NSAIDs vs. no NSAIDs (13.6% vs. 13.4%). The quantitative analysis did not show significant differences between NSAIDs vs. no NSAIDs administration (RR 1.49; 95% CI 0.81–2.75; $p = 0.19$) (Fig. 2). The prediction lower and upper limits were 0.19 and 11.65, respectively. The heterogeneity was high ($I^2 = 88.0\%$, 95% CI 75–94%; $p < 0.01$) and $\tau^2 = 0.449$. The sensitivity analysis showed the robustness of these findings in terms of point estimation, relative confidence intervals, and heterogeneity. Using the GRADE tool, we rated the quality of evidence for AL as moderate mainly because of limitations in study design (Supplementary Table 2).

Discussion

This study indicates that postoperative NSAIDs administration in the setting of upper GI surgery seems not associated with increased risk for AL. No robust data exist for GIB and AKI while any presumed correlation with NSAIDs mandates future focused trials.

ERAS protocols have been widely introduced into surgical practice across a variety of surgical fields [13]. In the setting of upper GI surgery perioperative optimization, expedient return to baseline mobility, fluid balance, early mobilization, prompt oral feeding, and adequate postoperative pain control have been implemented [14–16, 38, 39]. To attain an optimal opioid-sparing pain control, multimodal analgesic approaches have been proposed based on NSAIDs administration. In this direction, several studies reported an important increase in NSAIDs utilization for pain control after upper GI surgery [32–37]. The pharmacological mechanism of NSAIDs is related to the suppression of the cyclooxygenase (COX) enzyme resulting in prostaglandins (PGs) synthesis inhibition [40–42]. Specifically, the analgesic effect of NSAIDs is related with PGE2 and PGI2 synthesis suppression both involved in central and peripheral nociceptive responses. The reduced PGs synthesis is even associated with the related anti-inflammatory and anti-pyretic effect. Interestingly, it has been argued in previous studies a theoretical supplementary effect of NSAIDs on tissue healing [43–46]. Specifically, there is experimental evidence that COX-produced PGs modulate fibroblast growth factor-beta (β-FBF) and vascular endothelial growth factor (EGF) [47, 48]. Fibroblast, epithelial cells migration, and neo-angiogenesis are critical component of tissue healing. Previous experimental studies performed in mice models reported a decreased recruitment and migration of fibroblast, myofibroblast and epithelial cells at the anastomotic site with consequent altered collagen deposition, delayed anastomotic healing and reduced tissue strength [43–46]. Therefore, tissue healing at the anastomotic site might be theoretically altered by NSAIDs. Several studies focused on elective colorectal resections, described a strong association with postoperative NSAIDs use and AL. Specifically, Klein et al., reported an almost seven-fold increase in AL rate (OR 7.2, 95% CI 3.8–13) for patients assuming diclofenac after colonic resection for cancer [49]. Similarly, two recent meta-analyses by Kastora et al. [50], Modasi et al. [51] and Smith and colleagues [52] stated that colo-colic anastomoses appear to be more sensitive to AL thus recommending caution with NSAIDs utilization. However, the topic is intensely debated while other recent meta-analyses reported no significant association with AL [53, 54].

In our study, focused on upper GI surgery and esophageal/gastric anastomosis, we did not find any significant

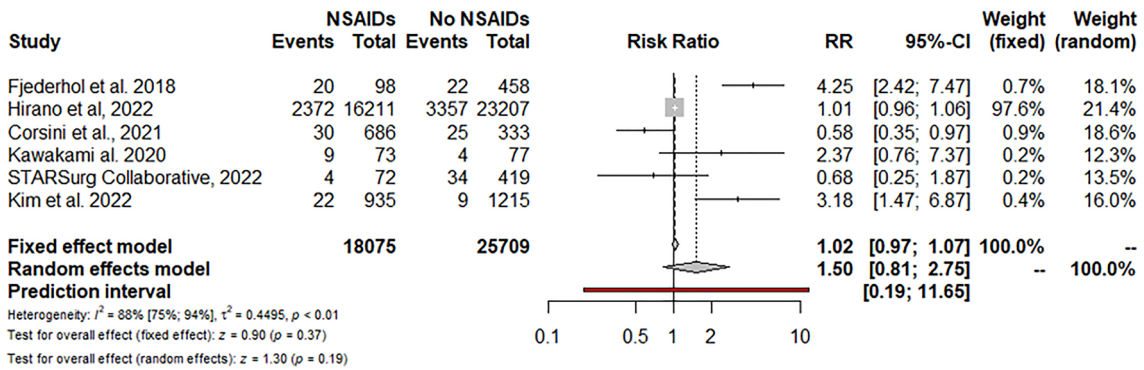

Fig. 2 Forrest plot for anastomotic leak. *RR*, risk ratio; *95% CI*, confidence interval

differences in terms of postoperative AL for NSAIDs vs. no NSAIDs administration (RR 1.49; 95% CI 0.81–2.75; $p=0.19$). Interestingly, the sensitivity analysis supported the robustness of this finding. This is similar to what recently reported by Hirano et al. that, in their dataset study from the Japanese nationwide database, reported no difference in term of AL when comparing NSAIDs vs. no NSAIDs administrations after elective esophageal resections (15% vs. 14%; $p=0.644$) [36]. Similarly, Corsini et al. in a retrospective cohort study of 1016 patients (2006–2018) from a high-volume cancer center also showed that NSAID use was not associated with AL after esophagectomy (OR 0.99; $p=0.958$) despite the significant increase in term of NSAIDs utilization during the study period [34]. By contrast, a previous cohort study showed a strong association between early NSAIDs use and AL with an almost fivefold increased risk after elective esophageal resection (OR 5.24, 95% CI 1.85–14.8) [32]. Similarly, Kim and colleague recently described their experience with 2150 patients undergoing laparoscopic gastrectomy. The authors reported a significantly higher AL rate in patients assuming NSAIDs in the early postoperative period (2.4% vs. 0.7%; $p=0.002$) [37]. While our results are based on a relatively large patient sample, their interpretation should be cautious because the remarkable heterogeneity ($I^2=88\%$) and possible confounders related to lack of standardized anastomotic techniques, preoperative patient selection, age and comorbidities, smoking status, neoadjuvant treatment, surgical approach (open vs. minimally invasive), operating surgeon experience, hospital volumes, anastomotic technique (hand-sewn vs. stapled), anastomosis location, blood flow assessment with indocyanine green, NSAIDs treatment duration, daily dose (mg/day), type of administered NSAIDs (i.e. flurbiprofen, diclofenac, ketorolac, loxoprofen, etc.), selective (celecoxib) or non-selective pharmacodynamics, oral/intravenous administration, and multimodal analgesia protocols (i.e. epidural catheters).

Gastrointestinal bleeding is a potential drawback of NSAIDs treatment. Bleeding may necessitate additional endoscopic or surgical intervention with longer length of stay and increased costs. The mechanism is related to the effect on thromboxane A2 (TXA2) that is an agonist for circulating platelet activation [55]. NSAIDs decrease PGs synthesis with direct interference on arachidonic acid (AA) metabolism and consequent reduced TXA2 synthesis. By preventing TXA2 production, platelet aggregation is inhibited with a potential increase in bleeding rate. In our preliminary analysis no differences were found in term of postoperative GIB. This is similar to Hirano and colleagues that described no differences (0.3% vs. 0.4%; $p=0.242$) [36] while Kim et al. stated higher rates of gastrointestinal bleeding (2.1% vs. 0.7%; $p=0.005$) in patients assuming NSAIDs [37]. Again, no differences were found in terms of NSAIDs induced AKI. This is similar to what described by Hirano et al. (0.6% vs. 0.7%; $p=0.26$) [36] and Kawakami et al. (1% vs. 1%; $p=$ ns) [33] that reported comparable rates of AKI. Notably, a robust quantitative synthesis was not practicable since studies are few and data sparce. Therefore, evidence is unclear while future trials are warranted to shed the light onto these topics.

To the best of our knowledge, this is the first meta-analysis analyzing the association between NSAIDs administration and AL in the setting of esophago-gastric surgery. We acknowledge several limitations, particularly those commonly discussed in the meta-analysis including observational studies. First, the large majority of studies did not have the standardized protocols for surgical techniques and perioperative analgesic protocols. Second, because different formulations and heterogeneous treatment duration our results might not be generalizable while a possible dose–response relationship could not be excluded. Third, the definitions and classifications of AL varied between included articles. Finally, we were not able to assess the hospital volume and experience of operating surgeons.

Conclusions

NSAIDs administration for postoperative analgesia seems not associated with an increased risk for AL after esophagogastric surgery. NSAIDs could be safely employed in the postoperative period as key component of multimodal analgesia for pain control in the setting of upper GI surgery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13304-023-01515-6.

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Author contributions AA, MM, JG and GG did the literature search. AA, GB, and DB formed the study design. Data collection done by AA, MM, FL, and MC. AA and GB analyzed the data. AA, GC, and DB interpreted the data. AA wrote the manuscript. All authors critically reviewed the manuscript.

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Data availability Data generated at a central, large-scale facility, available upon request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval For this type of article, ethical approval is not required because does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate For this type of study, formal consent was not necessary.

Research involving human participants and/or animals Research involved animals and humans. There is no consent required.

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