INTRODUCTION
Oncological breast surgery, classified as breast conserving surgery, oncoplastic surgery, and mastectomies (standard or with tissue sparing and reconstruction), are burdened with an overall complication rate up to 33%. Aquacel Ag Surgical is a combined hydrofiber-hydrocolloids dressing. The aim of this study is to evaluate the incidence of surgical site complications in patients presenting with three or more risk factors (or two, of which at least one classified as “high risk”), undergoing breast cancer surgery with/without reconstruction, comparing advanced (Aquacel Ag Surgical) with traditional dressing.

Methods: This is a retrospective, monocentric, case-control study based at the breast unit of the Città della Salute e della Scienza Hospital of Turin, Italy. Forty-two patients who underwent breast surgeries and met the inclusion criteria were enrolled, from February 1 to July 31, 2018. The primary endpoint was comparing the incidence of surgical site complications (skin alterations, infection, and wound dehiscence) in the two groups. The secondary endpoints were evaluating patient’s quality of life, aesthetic outcomes, and compliance to the dressings.

Results: The distribution of risk factors at the baseline between the two groups was balanced, without statistically significant differences. Wound complications’ incidence at 1 week was lower in the advanced dressing group (P = 0.015). On the bivariate descriptive analysis, advanced dressing proved to be easier to remove for the operator (P = 0.026). The aesthetic outcomes vouched for better scores in the advanced dressing group.

Conclusion: In the presented study Aquacel Ag Surgical dressing reduces surgical site complications in the first week after surgery in patients affected by three or more risk factors (or two with at least one classified as “high risk”). (Plast Reconstr Surg Glob Open 2021;9:e3911; doi: 10.1097/GOX.0000000000003911; Published online 18 November 2021.)

Disclosure: The authors have no financial interest to declare in relation to the content of this article.
provides a waterproof antiviral and antibacterial barrier (when intact and with no leakage).12–14

The aim of this study was to investigate the effect of Aquacel Ag Surgical on the overall surgical site complications in patients with more than three risk factors (or two factors, of which at least one considered at high risk) undergoing surgery for breast cancer, compared with the traditional dressing.

MATERIALS AND METHODS

We performed a retrospective, monocentric, case-control study, based at the breast unit of the Città della Salute e della Scienza Hospital of Turin, Italy. Our institution made available 21 Aquacel Ag Surgical dressings to be applied after breast surgeries from February 1 to July 31, 2018. We then compared the outcomes of the 21 patients treated with advanced dressing (cases), collected prospectively depending on the number and type of risk factors which they presented preoperatively, with the same number of patients presenting with the same inclusion/exclusion criteria and superimposable overall characteristics, previously treated in our breast unit with traditional dressing (controls), evaluated retrospectively. Patients were extensively informed about the different characteristics between the two dressings, stressing that the postsurgical treatment and follow-up would have been the same independently from the type of dressing chosen. The choice was finally left to each patient. All patients signed an informed consent form, including consent for the taking of image records, and the study was conducted in good clinical practice according to the Helsinki Declaration of 1975 and subsequent modifications.

In breast surgery, surgical incisions usually heal by primary intention. This type of surgery is subclassified as “clean.”71–75 The former classification is used in conjunction with the American Society of Anaesthesiology (ASA) score and surgery duration, which vary depending on patient’s and procedure’s characteristics respectively, in identifying those at risk for surgical site infections (SSIs).19,20

We selected preoperative risk factors for surgical site complications in breast surgery from a review of the literature.21–22 Risk factors were divided between patient-related factors: age (≥65 years), BMI (≥30 kg/m²), breast conformation (cup, size, and ptosis), smoking, diabetes, hypertension, chronic corticosteroid therapy, peripheral artery and liver diseases, neo-adjuvant chemotherapy, and neoadjuvant radiation therapy; and surgery-related factors: previous surgery (≤30 days or >30 days), extensive surgical undermining (level-2 OPS and nipple–areola complex sparing and skin reducing mastectomies), type of reconstruction (one stage implant-based reconstruction), use of acellular dermal matrices, and autologous reconstruction.3,25 Among the factors previously listed, BMI of 30 kg per m² or greater, radiotherapy, cup size of D or greater plus ptosis stage E or greater,26 surgery performed at 30 days or less, smoking, chronic corticosteroid therapy, extensive surgical undermining, use of acellular dermal matrix, and one stage implant-based reconstruction were classified as “high risk” factors.27

We offered Aquacel Ag Surgical (advanced dressing) to 21 patients presenting with more than three of the aforementioned risk factors (or two factors of which at least one was classified as “high risk”) instead of the traditional dressing, which consisted of Steri-strip (3M, St. Paul, Minn.), sterile gauze, and adhesive pad.

Exclusion criteria were T4 and/or M1 cancers according to TNM classification, allergies to the components of the Aquacel Ag Surgical, dermal hyperactivity (atopic dermatitis and detrital dermatitis), and age younger than 18 years old. All surgeries were performed by the same surgical team (general and plastic surgeons, AA and PMF respectively) employing the same techniques: BCS, OPS, tissue-sparing (nipple–areola sparing, skin-sparing and skin-reducing mastectomies), and simple mastectomies were performed based on each patient’s anatomical characteristics and oncological/reconstructive treatment goals. All patients received preoperative weight-based antibiotics (Cefazoline 2 g intravenous) with appropriate intraoperative re-dosing. ChloraPrep (CareFusion Corporation, San Diego, Calif.) was used for skin prepping, and oral antibiotics were continued postoperatively until drain removal.

A team formed by a general surgeon and breast nurse regularly assessed the conditions (oncological and aesthetic) of all patients at the follow-up visits on days 7, 30, and at 6- and 24-months postsurgery. Both dressings were placed at the end of the surgery in the operating room and removed at the first outpatient visit, 7 days after the surgery (unless an earlier change was needed).

The advanced dressing is sterile. Of the traditional dressing, only steri-strips and gauzes are sterile. After the initial removal, in both groups, dressings were changed for the same adhesive pad. During the first outpatient visit, an evaluation questionnaire was administered. The patient’s quality of life was evaluated using Body Image Scale (BIS) and Short Form 36 (SF-36) questionnaires: BIS was administered 30 days after surgery, whereas SF-36 was administered 6 months after the surgery. Scar and overall aesthetic outcomes were evaluated with Breast-Q questionnaire, which was administered 24 months after the surgery.
The evaluated postsurgical complications were skin alterations (erythema, maceration, and ischemia around the scar), infection and wound dehiscence. Infection was defined as (1) purulent drainage from the incision; (2) local positive culture swabs; (3) signs or symptoms of systemic infection. Suction drains were removed once the output was less than 30 ml (not hematic) over 24 hours. Study design is shown in Figure 1.

Study Endpoints

The primary endpoint was to investigate the effect of Aquacel Ag Surgical on the overall surgical site complication (skin alterations, infection, and wound dehiscence) rate in patients with more than three risk factors, or two factors of which at least one is classified as “high risk,” undergoing surgery for breast cancer, compared with traditional dressing; secondary endpoints were to evaluate the patient’s quality of life and overall aesthetic outcomes and compliance to the dressing.

Statistical Methods

Descriptive statistics for continuous variables were expressed as median (IQR), whereas for categorical, as absolute/relative frequencies. The impact of all risk factors has been tested using the Fisher exact test for categorical variables and the Mann-Whitney test for continuous ones. All reported $P$ values were obtained by the two-sided exact method, at the conventional 5% significance level. Data were analyzed as of October 2020 by R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

A total of 39 patients were evaluated, with all women having a median age of 66.1 (range 46–83). The advanced dressings group included 21 patients, whereas the traditional dressings group only 18 patients (three patients of the latter did not complete the follow-up). Fifteen patients (71.4%) in the advanced dressing group and 11 (61.1%) in the traditional dressing group were aged over 65 years. Distribution of risk factors at the baseline did not present statistically significant differences between the two groups; therefore, the population resulted balanced at the baseline. Baseline characteristics are shown in Table 1, Figure 2 and Figure 3. Number of surgical procedures divided by type in each group are reported in Table 2. No allergic reactions to the components of the advanced dressing occurred. None of the patients had to change dressings before the scheduled 7-day follow-up. Drains placed on patients undergoing BCS and simple mastectomy were removed without complications within 7 days after surgery on average, whereas those placed on patients undergoing oncoplastic surgery and mastectomies with reconstructions within 14 days on average. The hospital stay was 1 day for patients undergoing BCS and 2 days for the remaining patients.

In the presented study, there were no significant differences in patient-reported VAS values referring to dressing removal. Furthermore, no significant differences in the dressing tolerability during patients’ daily activities were found, while on the bivariate descriptive analysis, advanced dressing proved to be easier to be removed for the operator compared with the traditional dressing [IQR traditional dressing 3(5-2), IQR advanced dressing 2(3-1), $P = 0.026$].

No cases of SSIs occurred in the presented population. At the first follow-up visit (7 days), surgical wounds were healed in 20 patients in the advanced dressing group (95.2%), and in 11 patients in the traditional dressing one (61.1%), whereas, one patient (4.8%) from the advanced dressing group and seven patients (38.9%) from the control group showed complications of the surgical wound ($P = 0.015$). One patient (5.5%) in the control group, who developed a major suture dehiscence, required the use of a negative pressure wound therapy with VAC therapy (KCI an Acelity company, San Antonio, Tex.) for 15 days and then 5 days of hydrofiber dressing

Fig. 1. Study design. SF 36: Short Form 36.
Aquacel Extra (ConvaTec, Princeton, N.J.) for complete healing. At 1 and 6 months after surgery, differences in surgical site complications tended to overlap in the two groups \((P = 0.586\) and \(P = 0.462\), as shown in Fig. 4) and on average the complicated wounds healed completely after 1 month. The distribution of the complications and of the ASA score between patients who developed adverse events in the two groups is shown in Table 3.

At the end of the follow-up period (24 months), patient subjective evaluation of the aesthetic outcomes proved satisfactory in almost all cases, independently from the type of dressing. The analysis of the responses to Breast-Q, SF-36, and BIS revealed comparable aesthetic satisfaction of the patients both with regard to the surgical scar and with the more general body perception after surgery in both groups, without significant differences.

Investigator objective evaluation showed overall no significant difference between the two groups, although better scores were registered in the advanced dressing group compared with the control group.

**DISCUSSION**

In breast surgery, there is a unique combination of expected outcomes: the oncological safety and the aesthetic result. Prevention of complications in breast surgery mainly affects patient’s quality of life, reduces delays in adjuvant therapies, and can affect the costs of the health system in the long run.\(^2^9\) The incidence of complications varies greatly, depending on the type of surgery and on the number and type of risk factors.\(^2^9\)–\(^3^2\)

Surgical complications can be influenced by patient’s risk factors, type of surgery (conservative versus radical), and surgical techniques; postoperative management (including types of dressings, dressing change timing, drain duration, and patient daily habits) can influence surgical complications too, and it is connected to the type of dressing. There are many different types of dressings available, but finding “one size fits all” is impossible due to the specific characteristics of different surgical wounds. The four main goals are better wound healing, scar aesthetic outcome, patient’s compliance and overall quality of life, and lower SSI incidence.

In 2016 a Cochrane review showed that there is low to very low certainty evidence that wound exposure or any dressing reduces or increases the risk of SSIs compared with alternative options investigated.\(^3^3\) Li et al showed with a systematic review and meta-analysis of randomized controlled trials that silver-containing dressings were not associated with lower incidence of SSIs, although the quality of the studies analyzed was very low.\(^3^4\)
Aquacel Ag Surgical is widely used in various surgical specialties, mainly in orthopedic, plastic and reconstructive surgery, abdominal surgery and cardio-thoracic surgery, with considerable benefits in terms of both lower incidence of surgical site complications and greater patient satisfaction. Springer et al conducted a randomized clinical trial, including 262 patients undergoing primary total hip arthroplasty or primary total knee arthroplasty, divided into traditional surgical dressing (Primapore, Smith & Nephew, London, UK) group or advanced occlusive dressing (Aquacel Ag, ConvaTec, Princeton, N.J.) group: the use of occlusive antimicrobial barrier dressings significantly reduced wound complications and dressing changes and improved overall patient satisfaction. Bocchiotti et al compared two groups of patients undergoing thigh lift in a case-control study (traditional versus Aquacel Ag Surgical). Aquacel Ag Surgical appeared to be more comfortable and easier to manage for the patient, durable, waterproof, and nontraumatic when changed. Unlike the presented study, in which patients with a different combination of risk factors were selected to be treated with Aquacel Ag Surgical, they excluded patients who smoked and who showed cardiovascular and dysmetabolic diseases.

The only study describing the use of Aquacel Ag Surgical in the setting of breast surgery was conducted by Struik et al, including 230 patients performing an intention-to-treat basis analysis: Aquacel Ag Surgical dressing approximately reduces 50% of the incidence of wound infections compared with traditional dressing (RR 0.51), although without a significant difference.

Table 2. Number of Surgical Procedures Divided by Type in each Group

| Type of Surgery          | BCS | SM | SSM | NSN | OPS | BiOS |
|-------------------------|-----|----|-----|-----|-----|------|
| Advanced dressing (no. patients) | 11  | 8  | —   | 1   | 1   | —    |
| Traditional (no. patients)      | 12  | 4  | 1   | —   | —   | 1    |

SM: simple mastectomy; SSM: skin-sparing mastectomy; NSM: nipple–areola sparing mastectomy; BiOS: bilateral surgery consisting in right OPS and left SM.
Table 3. Characteristics of Patients Who Developed Complications of the Surgical Wound in the Two Groups

| Type of Dressing | Type of Surgery | Type of Complication | ASA Score | No. Risk Factors | Type of Risk Factors |
|------------------|-----------------|----------------------|-----------|------------------|---------------------|
| Advanced dressing | OPS (n-BCS)      | Maceration of pericrycatric skin | II        | 3                | Breast ptosis, extensive undermining, large breast size |
| Traditional dressing | SM (n-BCS)      | Pericrycatric ischemic area and dehiscence | IV        | 8                | HIA, diabetes, BMI > 30 kg/m², cardiovascular disease, breast ptosis, large breast size, age > 65 y, liver disease |
| Traditional dressing | SM (n-BCS)      | Maceration of pericrycatric skin | III       | 6                | BMI > 30 kg/m², smoke, breast ptosis, large breast size, extensive undermining, previous breast surgery (<30 days before) |
| Traditional dressing | SM (n-BCS)      | Dehiscence | III       | 4                | HIA, diabetes, age > 65 y, prior radiotherapy |
| Traditional dressing | SM (n-BCS)      | Skin erythema of the margins, swelling, and local pain | II        | 2                | Age > 65 y, prior radiotherapy |
| Traditional dressing | BCS             | Skin erythema of the margins, swelling, local pain, and low exudate | II        | 4                | BMI > 30 kg/m², HIA, breast ptosis, large breast size |
| Traditional dressing | BCS             | Skin erythema of the margins, swelling, local pain, and low exudate | III       | 6                | Diabetes, age > 65 y, HIA, breast ptosis, large breast size |
| Traditional dressing | BCS             | Maceration of pericrycatric skin, skin erythema of margins, and dehiscence | II        | 4                | breast ptosis, large breast, HIA, BMI > 30 kg/m² |

SM: simple mastectomy; HIA: hypertension; ASA: American Society of Anaesthesiologists.

However, they detected a significant improvement in patient satisfaction, reduction in dressing changes and wound-related costs, using Aquacel Ag. Unlike Struik, we performed a subclassification of patients’ risk factors to select those in which the use of an advanced dressing could be more indicated and useful; we evaluated the aesthetic results of the scar and the quality of life of the patients with objective assessment tools and elongated the follow-up duration accordingly. We also included patients who performed plastic surgery procedures for reconstruction and who underwent neoadjuvant chemotherapy.

Ferrando et al, in a population study, classified risk factors between patient- and surgery-related, some of which were classified as “high risk.” In patients presenting with a variable combination of up to three patient- and/or surgery-related risk factors, with at least one classified as “high risk,” closed incision negative pressure therapy proved capable of reducing the incidence of overall complications and wound dehiscence, with statistical significance. In the presented study, the authors adopted the same classification of risk factors. However, we are aware that a dressing, even if advanced, cannot act by reducing all the complications of the surgical site, as the surgical technique and the type of intervention have the greatest influence. Nevertheless, we believe that choosing a specific dressing based on the displayed risk factors can contribute to a better surgical outcome. Advantages of the presented study compared with those assessed above are the trial design (case-control), the duration of the follow-up (24 months), and the use of objective assessment tools for evaluating the aesthetic outcome and quality of life (BIS; SF-36 and Breast-Q). Because advanced dressing has a higher cost compared with traditional dressing, we studied patients presenting with a combination of risk factors for surgical wound complications, to understand which patient could benefit the most from an advanced dressing, thus justifying the higher cost of the product. The limitations of the study are that the sample was small, the study was not randomized, and that we did not subgroup for the different surgical techniques.

CONCLUSIONS

The authors showed in this study that, in the presence of three or more risk factors (or two, with at least one classified as “high risk”) between those considered, the use of Aquacel Ag Surgical dressing in patients undergoing surgery for breast cancer was associated with a statistically significant reduction in overall surgical site complications in the first week after the surgery, excluding infections that were not found in the presented population. The dressing was well tolerated and kept in place for the expected time, with no need for outpatient visits other than those regularly scheduled. However, further randomized trials are needed to confirm these results.

A. Nicotera, MD
Department of General and Specialistic Surgery
AOU Città della Salute e della Scienza
Turin, Italy
E-mail: antonella.nicotera@gmail.com

REFERENCES
1. Vitug AF, Newman LA. Complications in breast surgery. Surg Clin North Am. 2007;87:431–451. x.
2. Sullivan SR, Fletcher DRD, Isom CD, et al. True incidence of all complications following immediate and delayed breast reconstruction. Plast Reconstr Surg. 2008;122:19–28.
3. Hultman CS, Daiza S. Skin-sparing mastectomy flap complications after breast reconstruction: review of incidence, management, and outcome. Ann Plast Surg. 2009;50:249–55; discussion 255.
4. Carlson GW, Bostwick J III, Styblo TM, et al. Skin-sparing mastectomy. Oncologic and reconstructive considerations. Ann Surg. 1997;225:570–575; discussion 575.
5. Padubidri AN, Yetman R, Browne E, et al. Complications of post-mastectomy breast reconstructions in smokers, ex-smokers, and nonsmokers. Plast Reconstr Surg. 2001;107:342–349; discussion 350.
6. Munhoz AM, Arruda E, Montag E, et al. Immediate skin-sparing mastectomy reconstruction with deep inferior epigastric
perforator (DIEP) flap. Technical aspects and outcome. *Breast J.* 2007;13:470–478.

7. Macedo FO, Bergmann A, Koifman RJ, et al. Axillary surgery in breast cancer: acute postoperative complications in a hospital cohort of women of Rio de Janeiro Brazil. *Mastology* 2018;28:80–86.

8. Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. *Breast.* 2017;36:67–73.

9. Nascimento de Carvalho F, Bergmann A, Koifman RJ. Functionality in women with breast cancer: the use of International Classification of Functioning, Disability and Health (ICF) in clinical practice. *J Phys Ther Sci.* 2014;26:721–730.

10. Bergmann A, Mendes VV, de Almeida Dias R, et al. Incidence and risk factors for axillary web syndrome after breast cancer surgery. *Breast Cancer Res Treat.* 2012;131:987–992.

11. Bocchiotti MA, Baglioni EA, Spaziante L, et al. Aqueous surgical dressing after thigh lift: a case-control study. *Plast Reconstr Surg Glob Open.* 2016;4:e806.

12. Jones SA, Bowler PG, Walker M, et al. Controlling wound bioburden with a novel silver-containing Hydrofiber dressing. *Wound Repair Regen.* 2004;12:288–294.

13. Bowler PG, Jones SA, Walker M, et al. Microbicidal properties of a silver-containing hydrofiber dressing against a variety of burn wound pathogens. *J Burn Care Rehabil.* 2004;25:192–196.

14. Bowler PG. Progression toward healing: wound infection and the role of an advanced silver-containing Hydrofiber dressing. *Ostomy Wound Manage.* 2003;49:2–5.

15. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470–485.

16. Bertin ML, Crowe J, Gordon SM. Determinants of surgical site infection after breast surgery. *Am J Infect Control.* 1998;26:61–65.

17. Throckmorton AD, Boughley JC, BOOSTROM SY, et al. Postoperative prophylactic antibiotics and surgical site infection rates in breast surgery patients. *Ann Surg Oncol.* 2009;16:2464–2469.

18. Corcione S, Lupia T, De Rosa FG. Skin and soft tissue infections after breast surgery. *Curr Open Infect Dis.* 2019;3:87–94.

19. Omekwu I, Yakkanti R, Protzer L, et al. Surgical wound classification and surgical site infections in the orthopaedic patient. *J Am Acad Orthop Surg Glob Res Rev.* 2017;1:e022.

20. *Surgical Site Infection (SSI) Event.* Center for Disease Control. 2010. http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSICurrent.pdf?agreement=yes&next=Accept. Updated March 2020. Accessed May 2, 2020.

21. de Blacan C, Ogunleye AA, Momoh AO, et al. High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the national surgical quality improvement program database. *Ann Surg.* 2012;255:551–555.

22. Sørensen LT, Hørsby J, Friis E, et al. Smoking as a risk factor for wound healing and infection in breast cancer surgery. *Eur J Surg Oncol.* 2002;28:815–820.

23. Stannard JP, Atkins BZ, O’Malley D, et al. Use of negative pressure therapy on closed surgical incisions: a case series. *Ostomy Wound Manage.* 2009;55:58–66.

24. Grier L, Mattos D, Mastroianni M, et al. Assessment of patient factors, surgeons, and surgeon teams in immediate implant-based breast reconstruction outcomes. *Plast Reconstr Surg.* 2015;135:245e–252e.

25. Kim DY, Park SJ, Bang SI, et al. Does the use of incisional negative-pressure wound therapy prevent mastectomy flap necrosis in immediate expander-based breast reconstruction? *Plast Reconstr Surg.* 2016;138:558–566.

26. Kirwan L. A classification and algorithm for treatment of breast ptosis. *Aesthet Surg J.* 2002;22:555–563.

27. Ferrando PM, Ala A, Busone R, et al. Closed incision negative pressure therapy in oncological breast surgery: comparison with standard care dressings. *Plast Reconstr Surg Glob Open.* 2018;6:e1732.

28. Lee K, Jung JH, Mun GH, et al. Influence of complications following total mastectomy and immediate reconstruction on breast cancer recurrence. *Br J Surg.* 2020;107:1154–1162.

29. De La Cruz L, Blankenship SA, Chatterjee A, et al. Outcomes after oncoplastic breast-conserving surgery in breast cancer patients: a systematic literature review. *Ann Surg Oncol.* 2016;23:3247–3258.

30. Corban J, Shah H, Safran T, et al. A systematic review of complications associated with direct implants vs. tissue expanders following Wise pattern skin sparing mastectomy. *J Plast Reconstr Aesthet Surg.* 2017;70:1191–1199.

31. Colwell AS, Christensen JM. Nipple-sparing mastectomy and direct-to-implant breast reconstruction. *Plast Reconstr Surg Reconstructive* 2017;140(5S Advances in Breast Reconstruction):44S–50S.

32. Bennett KG, Qi J, Kim HM, et al. Comparison of 2-years complication rates among common techniques for post mastectomy breast reconstruction. *JAMA Surg.* 2018;153:901–908.

33. Dumville JC, Gray TA, Walter CJ et al. Dressings for the prevention of surgical site infection. *Cochrane Database Syst Rev.* 2016;16:CD003091.

34. Li HZ, Zhang L, Chen JX, et al. Silver-containing dressing for surgical site infection in clean and clean-contaminated operations in total joint arthroplasty: a randomized controlled trial. *J Surg Res.* 2016;215:58–107.

35. Springer BD, Beaver WB, Griffin WL, et al. Role of surgical dressings in total joint arthroplasty: a randomized controlled trial. *Am J Orthop (Belle Mead NJ).* 2015;44:415–420.

36. Stryuk GM, Vrijland WW, Birnie E, et al. A randomized controlled trial on the effect of a silver carboxymethylcellulose dressing on surgical site infections after breast cancer surgery. *PLoS One.* 2018;13:e0195715.