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Biological welding enables rapid and efficient bladder cystotomy closure and reveals the underlying repair mechanism

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Abstract

Background： Bladder rupture repair surgery is limited by its long duration, significant blood loss, and complex procedures. Biological welding technology, which integrates multiple functions such as cutting, hemostasis, and tissue fusion, has shown potential in the field of soft tissue repair surgery but has not yet been widely explored in clinical applications for bladder rupture repair.

Method： This study used 32 adult male Beagle dogs to establish a bladder rupture model, randomly assigned to the biological welding group or the traditional suturing group. Outcomes assessed included surgical time, blood loss, postoperative inflammation, and hematuria. Histopathological analysis and RNA sequencing analysis were performed at multiple postoperative time points to evaluate the tissue recovery process and repair mechanisms.

Results： The results demonstrated that biological welding significantly reduced surgical time (21.80±4.79min vs. 75.15±13.26min, $p<0.001$) and intraoperative blood loss (6.37±0.89g vs. 30.36±6.59g, $p<0.001$) compared to traditional suturing. Postoperative complications, such as hematuria and inflammatory response, were notably lower in the biological welding group. Histopathological analysis revealed enhanced cell migration and tissue fusion in the biological welding group, leading to

accelerated bladder healing and reduced adhesions. Transcriptomic sequencing indicated that biological welding activated a limited number of immune-related genes and signaling pathways in the early postoperative period, facilitating rapid repair and a shorter duration of abnormal gene expression.

Conclusions： Our research indicates that biological welding technology demonstrates significant advantages in bladder rupture repair surgery, including enhanced surgical efficiency, reduced incidence of postoperative complications, and accelerated tissue healing process, with broad prospects for clinical application.

Keywords: Biological Welding, Bladder Rupture Repair, Mechanism Research; Surgical Efficiency

Background

Bladder repair is a complex surgical procedure targeting conditions with structural and functional impairments of the bladder. It plays a crucial role in the treatment of diseases such as bladder cancer, bladder exstrophy, urothelial injury of the bladder, bladder dysfunction, bladder trauma, and neurogenic bladder[1]. These conditions arise from congenital malformations, trauma, radiotherapy, chronic inflammatory diseases, or neurological disorders, and can lead to significant bladder dysfunction or even loss of bladder function[2-4]. Bladder repair surgeries, including cystectomy, bladder suturing, and urinary diversion, not only remove pathological tissues but also reconstruct bladder function. This helps patients regain urinary control, reduces complications, and significantly improves their quality of life[5-7].

The complexity of bladder repair surgery remains a challenge. Regardless of whether performed via open or minimally invasive approaches, suture-based techniques remain the core method for bladder repair. However, These methods may also lead to various postoperative complications, including bleeding, infection, and urine leakage, which require strict monitoring and timely medical intervention for proper management[8-11]. Additionally, individual differences among patients, such as diabetes or renal insufficiency, may further increase surgical risks and the incidence of postoperative complications[12,13]. Therefore, the pursuit of safer and more efficient bladder repair techniques has become particularly urgent.

Biological welding is a novel and cutting-edge surgical tool that integrates the functions of cutting, hemostasis, and welding into a single operation. It utilizes precise

high-frequency current pulses to simultaneously cut and coagulate soft tissues or achieve hemostasis and tissue fusion[14-16]. Clinical studies have shown that Biological welding can significantly reduce surgical and recovery times, as well as intraoperative blood loss[17-19]. For instance, studies by Dmytro have demonstrated that the application of Biological welding in the treatment of frontal sinus tumors can significantly shorten surgical time, reduce recovery time, decrease intraoperative blood loss, and lower the incidence of complications[17]. Our team's latest research demonstrates that biological welding technology has significant advantages in circumcision, including shortened surgical time, no bleeding, minimized thermal injury, and rapid recovery[20]. Overall, biological welding technology has shown its potential clinical application value in various surgical fields.

Despite its potential, Biological welding has not yet been widely applied in the research and practice of bladder repair. Therefore, the aim of this study is to break the mold by employing advanced Biological welding for bladder repair. We plan to establish an animal model of bladder rupture through open surgery and immediately perform biological welding repair on the model animals, comparing it with the commonly used suture-based technique. We expect that the adoption of Biological welding will enhance the safety and efficiency of bladder repair surgery, thus developing a new, safe, and efficient bladder repair technique to address the challenges currently faced in this field.

Materials and methods

Animal models

This study was carried out in strict accordance with the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) v2.0, ensuring rigorous reporting of experimental design, animal welfare, and statistical analysis. The protocol was approved by the the Animal Ethics Committee of the Daping Hospital of the Third Military Medical University（Ethical Number: Medical Research Review 2015-53）. The dogs used in this study were acquired from Chongqing Tengxin Biotechnology Co, Ltd. A total of 32 adult male Beagle dogs were used in this study and randomly assigned to the biological welding group and the control group (i.e., the traditional suturing group).

Baseline data, including age, body weight, blood routine, urine routine, and blood glucose as well as liver and kidney function, were meticulously analyzed and compared between the two groups. All experimental animals were maintained on a standardized diet and housed under identical conditions. The criterion for confirming the animal's death is that there are no vital signs (respiratory cessation, disappearance of corneal

reflex, and cessation of cardiac activity) for at least 5 minutes. This method complies with the requirements of the "Guide to Euthanasia for Animals" (2020) by the American Veterinary Medical Association and avoids the use of drugs prohibited in "Scientific Reports" (such as chloral hydrate, ether).

Surgical Procedures

Prior to the experiment, animals were fasted for 12 hours with water deprivation. Blood and urine samples were collected for routine blood tests, urinalysis, and biochemical examinations. Anesthesia was induced via intramuscular injection of 30 mg/kg sodium pentobarbital (3% solution). Routine hair removal and disinfection were performed, followed by the insertion of a urinary catheter through the urethra. The correct and safe placement of the catheter was confirmed by instilling normal saline through it. A vertical incision was made in the right lower abdomen in both groups, and the skin was sharply incised.

Then, inject normal saline (approximately 200 ml) into the bladder of each dog. During the injection process, make a mark at the 4–8cm position. Then, drain the normal saline at the marked position and perform resection to make the average incision length of each group similar. Although there were slight differences in the incision length, statistical analysis showed that there was no significant correlation between the specific incision length and outcomes such as blood loss or operation time.

In the biological welding group, a high-frequency current-based biological welding device was used. The bladder wound was fused under the pressure applied by the welding forceps in the welding mode (energy parameters: 21–138 V, frequency 450 Hz). In our experiments, the device was operated under a standardized setting: the welding equipment used the "welding" operation with energy (70 v -90v，450hz) for biologic welding to repair the bladder tissue and mucosa of beagle dogs. Specifically, during the operation, the surgeon applies the welding current for approximately 3 - 5 seconds. Due to the slight unevenness in the thickness of the beagle's bladder tissue, the output energy ranges between 70 v and 90 v.

The control group underwent traditional surgical procedures, with the bladder closure achieved using 3-0 absorbable polyglycolic acid (Vicryl) sutures for full - layer interrupted suturing. The abdominal cavity was closed using 3-0 absorbable sutures in both groups. Postoperatively, animals were administered 0.15 ml/kg of phenobarbital hydrochloride via intramuscular injection to promote recovery from anesthesia.

Animals were fasted for 4 hours after surgery and received intramuscular injections of gentamicin (1.2 mg/kg) twice daily for 1 week. Urine was collected 1 hour after surgery to observe hematuria. The catheter was removed 1 week postoperatively. All animals were randomly assigned to groups, and all surgeries were performed by the same team to standardize procedures. While it was not feasible to blind the surgeon to the intervention (because the techniques are very different), all post-operative assessments and data analyses (histopathology, biofluid analyses, sequencing) were performed by investigators blinded to group assignment.

Surgical Time, Temperature, and Blood Loss

The surgical time was recorded throughout the entire bladder repair process. During bladder anastomosis, the temperature at the anastomotic site was continuously monitored and recorded, with the highest temperature value being used as the temperature indicator for the anastomosis process. During the anastomosis, sterile dry gauze that had been pre-weighed was used to wipe away the blood that flowed out. After the anastomosis was completed, the gauze was weighed again, and the blood loss during the bladder anastomosis was calculated and recorded by subtracting its initial weight.

Pressure Test

The pressure test was performed in both groups after the completion of bladder closure. The urinary catheter was connected to a three-way tube, with the other end of the tube connected to an injection pump and a digital manometer. Using a 50-mL syringe, normal saline was injected into the bladder at a constant rate until the bladder was fully distended. When the manometer indicated a pressure of 100 cm H_2O, the anastomotic site was observed and recorded for any leakage.

Biofluid Analysis

Venous blood and urine samples were collected on postoperative days 1, 3, 5, and 7 for routine blood and urine examinations.

Histopathological Analysis

At 1, 2, 4, 8, and 12 weeks postoperatively, three Beagle dogs from each group were euthanized. The lower abdomen was subsequently opened to expose the bladder

for assessment of the healing status. A full-thickness bladder wall specimen measuring 1.5 cm × 1.5 cm was excised from the anastomotic site using surgical scissors and preserved in liquid nitrogen and 4% paraformaldehyde solution, respectively. The bladder samples preserved in 4% paraformaldehyde were subjected to graded dehydration after 24 hours, followed by paraffin embedding and hematoxylin-eosin (H&E) staining to observe the histopathological changes in tissues following different bladder anastomosis techniques.

Raman Spectrum Test

The fusion area of the bladder was analyzed using a Raman spectrometer (NTEGRA Spectra-II). A section was cut from the central region of the bladder tissue sample and rinsed with deionized water to remove the adhered damaged adipose tissue (which appeared as reddish-brown residue at this time). Raman spectra were collected from the central region, and multiple frequency points were obtained from each sample, and averaged to reduce signal noise. The obtained Raman spectral data were first edited and smoothed using Origin 2024 software. Subsequently, the baseline was eliminated through polynomial fitting, and the Raman spectral range was limited to 900 - 2000 cm−1. Finally, the Gaussian-Lorentz function was used to calibrate the characteristic peaks, from which information such as peak intensity was extracted.

Sequencing

At 1, 4, and 12 weeks postoperatively, bladder samples from the biological welding group and the control group (n = 3 per group) were collected and pooled for RNA extraction. Subsequently, a digital gene expression (DGE) sequencing library was constructed and sequenced on the Illumina HiSeq platform. The sequencing data underwent stringent quality assessment, with low-quality sequences being discarded. High-quality sequencing data were then subjected to in-depth bioinformatics analyses, including sequence alignment, gene expression level analysis, differential gene expression analysis, Gene Ontology (GO) enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical analyses were performed using GraphPad Prism. For comparisons between two independent groups, a two-tailed t-test was applied when data were normally distributed. Equal-variance or Welch’s t-test was used as appropriate based on variance homogeneity. For non-

normally distributed data, non-parametric tests were used. Comparisons among multiple groups were conducted using one-way analysis of variance (ANOVA) with appropriate post hoc testing. For longitudinal functional indices measured repeatedly over time (urinary red blood cell counts and urinary protein levels on days 1, 3, 5, and 7), a two-way repeated-measures ANOVA was performed, followed by Bonferroni-corrected post hoc pairwise comparisons. Statistical significance was set at $p < 0.05$; where multiple-testing adjustment was applied, adjusted p-values (padj) < 0.05 were considered significant.

Results

Biological welding Effectively Repairs Bladder Rupture

In this study, 32 healthy adult male Beagle dogs were randomly and evenly assigned to the biological welding group and the control group. To ensure the accuracy of the experiment, we compared the age and body weight of the Beagle dogs in both groups, and the results showed no significant differences between the groups (Fig. 1A-C). Furthermore, to further verify the health status of the Beagle dogs, we conducted venous blood tests, with indicators including blood glucose, liver function, and kidney function. The test results showed that these indicators were within the normal range for both groups of Beagle dogs, and there were no significant differences statistically (Fig. 1D-H). Collectively, these results indicate that all Beagle dogs involved in this study met the experimental requirements, providing a reliable basis for subsequent experimental operations and data analysis.

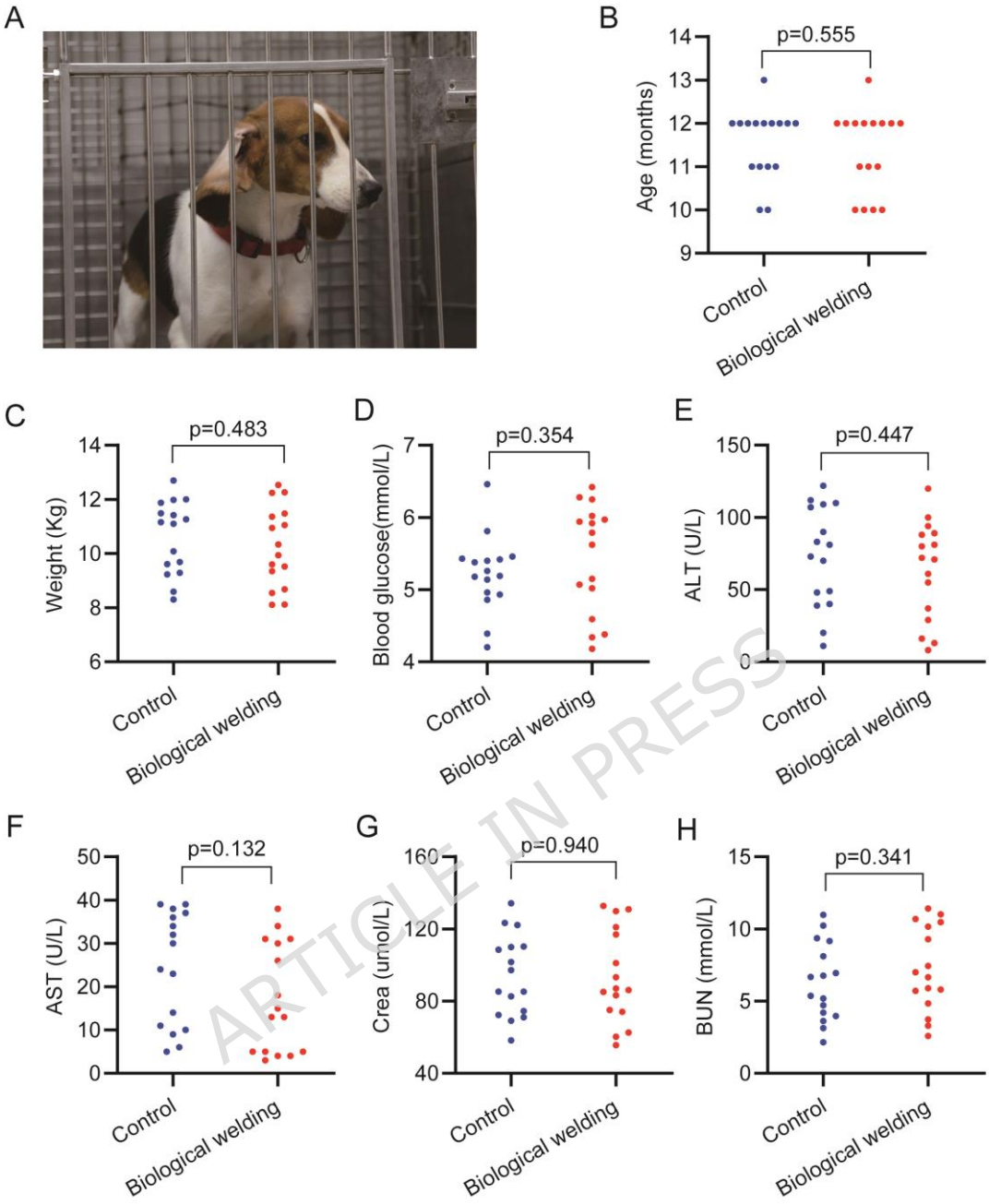

Figure 1 Basic characteristics of animals involved in this study. (A) Representative images of animals; (B) Age; (C) Body weigh; (D) Blood glucose; (E) Alanine aminotransferase (ALT, U/L); (F) Aspartate aminotransferase (AST, U/L); (G) Creatinine (μmol/L); (H) Blood urea nitrogen (BUN, mmol/L). n = 16.

After anesthesia was induced in both groups of animals, a urinary catheter was inserted through the urethra, and normal saline was instilled through the catheter to ensure its correct and safe placement. Using the same method for both groups, a bladder rupture model with a length of 4–8 cm was created in the Beagle dogs (Fig. 2A).

Subsequently, bladder repair surgery was performed, with the biological welding group undergoing intermittent welding to fuse the bladder using. Biological welding, while the control group underwent full - layer interrupted suturing traditional suturing techniques (Fig. 2B).

The presence of urine leakage is a key indicator for assessing the efficacy of bladder repair. In this study, urine leakage was observed in the postoperative, bladder-distended state, and no leakage was detected at the bladder anastomosis sites in either group (Fig. 2C), indicating a 100% success rate of anastomosis. Furthermore, the burst pressure at the repaired bladder site was measured, and the results showed that the burst pressure exceeded 100 cm H_2O (approximately twice the physiological pressure) (Fig. 2D). No wound rupture or urine leakage was observed in either the biological welding group or the control group. These findings demonstrate that Biological welding is as effective as traditional suturing techniques in repairing ruptured bladders.

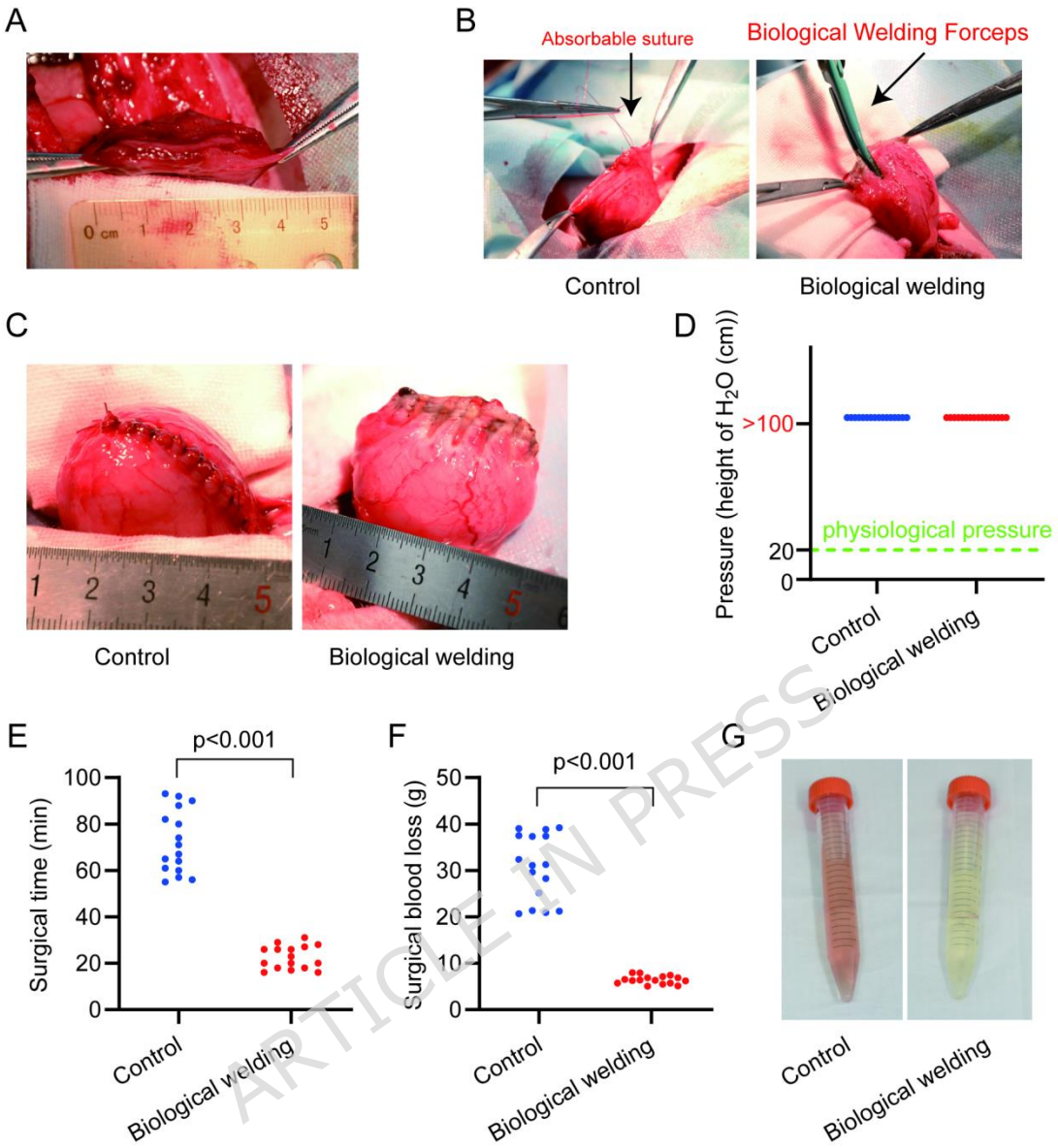

Figure 2 Biological welding effectively repairs the bladder. (A) Construction of the bladder rupture model; (B) Representative images of the bladder repair process; (C) Representative images of the bladder in the urine-distended state after repair; (D) Pressure test after bladder repair; (E) Surgical time for bladder repair; (F) Blood loss during bladder repair surgery. (G) Urine within 1 hour after bladder repair. n = 16.

Biological welding Reduces Surgical Time and Blood Loss

Surgical safety is a core indicator for evaluating surgical outcomes, particularly in terms of controlling surgical duration and managing intraoperative blood loss. Optimizing surgical time and blood loss is of decisive significance for enhancing surgical safety. In terms of surgical duration, the biological welding group had a

significantly shorter operative time of 21.80 ± 4.79 min compared to 75.15 ± 13.26 min in the control group ($p < 0.001$) (Fig. 2E). Regarding blood loss, the biological welding group exhibited significantly less blood loss of 6.37 ± 0.89 g during bladder repair, compared to 30.36 ± 6.59 g in the control group ($p < 0.001$) (Fig. 2F). Additionally, the color of urine within 1 hour postoperatively was observed, the control group had light red urine, while the biological welding group had light yellow urine (Fig. 2G). These data demonstrate the advantages of Biological welding over traditional suturing techniques, which not only reduces surgical time but also effectively minimizes intraoperative blood loss.

Biological welding Reduces Complications

Hematuria is a critical complication in the process of bladder repair. Therefore, this study measured the number of red blood cells (RBCs) in urine within 7 days postoperatively. The results showed that the RBC count in urine significantly decreased over time in both the biological welding group and the control group. However, at postoperative days 1, 3, 5, and 7, the RBC count in the urine of the biological welding group was significantly lower than that of the control group ($p < 0.05$) (Fig. 3A). Additionally, on postoperative day 1, three dogs in the biological welding group had no detectable RBCs in their urine, while all dogs in the control group exhibited RBCs. These findings indicate that Biological welding can effectively improve hematuria following bladder rupture repair.

Inflammatory response is one of the common complications after surgery. In this study, venous blood samples were collected from experimental animals on postoperative days 1, 3, 5, and 7 for routine blood tests. The results showed that there were no significant differences in RBC count and hemoglobin (HGB) levels between or within the groups during the 7 days postoperatively (Fig. 3B, C). However, both groups exhibited a significant increase in white blood cell (WBC) and neutrophil (GRAN) counts after surgery, which peaked on day 3 and then gradually decreased (Fig. 3D, E). This indicates that both biological welding and traditional suturing techniques induced inflammatory responses following bladder repair. In intergroup comparisons, the WBC and neutrophil counts in the biological welding group were significantly lower than those in the control group at all time points. These results suggest that Biological welding significantly reduces postoperative inflammatory responses compared with traditional suturing techniques.

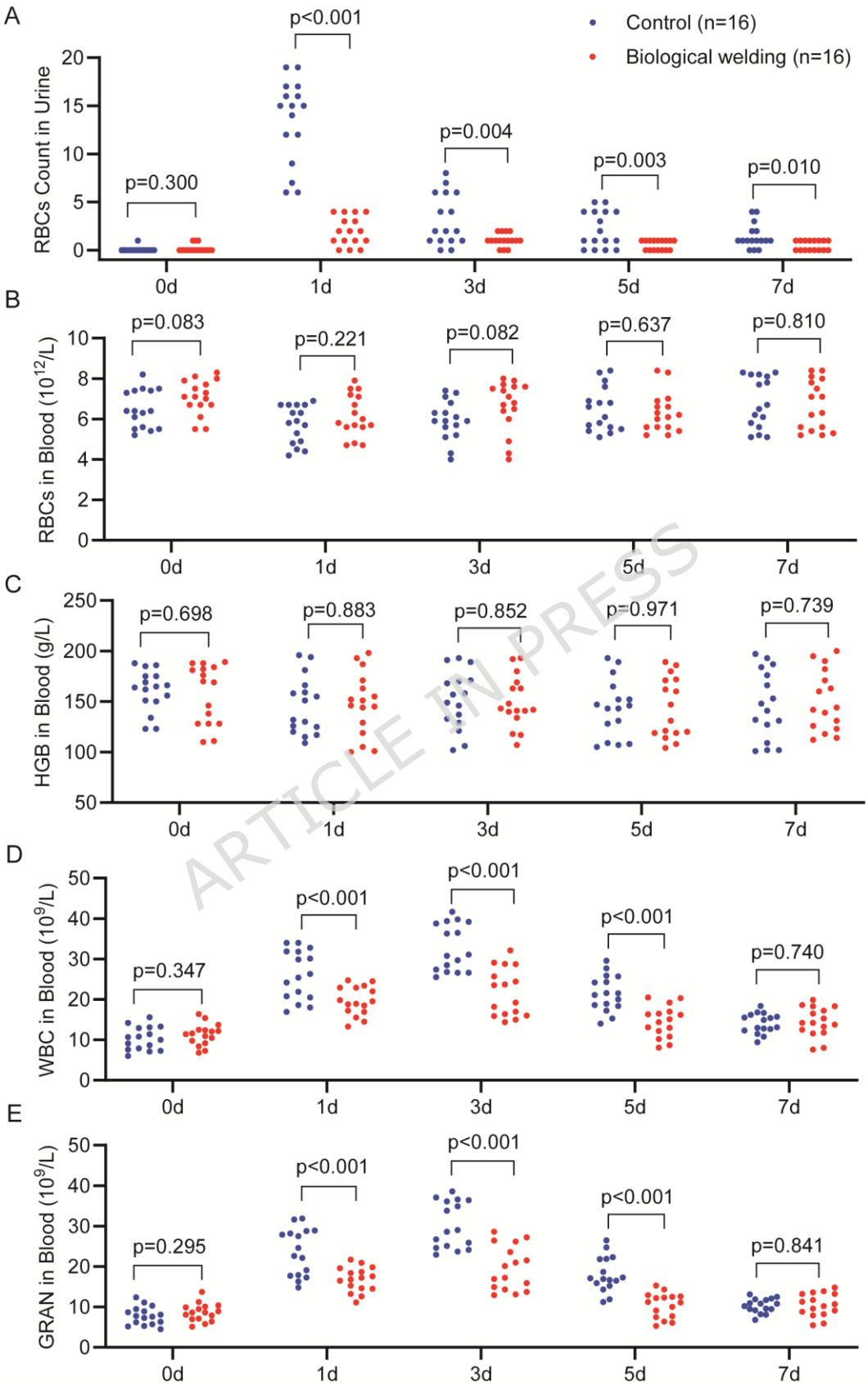

Figure 3 Postoperative biofluid analysis. (A) Number of red blood cells in urine; (B) Red blood cell count in blood; (C) Hemoglobin level in blood; (D) White blood cell

count in blood; (E) Neutrophil count in blood. n = 16. RBC per μL of urine.

Biological welding Promotes Tissue Fusion via Cell Migration

Histopathological staining techniques allow for detailed observation of the microscopic structure of wound healing. In this study, immediate postoperative hematoxylin and eosin (H&E) staining was performed on the welded bladder tissues. Pathological analysis revealed no significant structural changes in the bladder tissues of either the control or biological welding groups, with clear demarcations between the mucosal and muscular layers. Notably, the mucosal layers on both sides of the wound in the biological welding group were completely fused (Fig. 4A), indicating good wound closure.

In terms of injury assessment, mild thermal and pressure injuries were observed in the outer membrane layer of the bladder tissues in the welding group, whereas no such injuries were detected in the control group (Fig. 4A). This suggests that Biological welding has a minor adverse effect on tissue fusion.

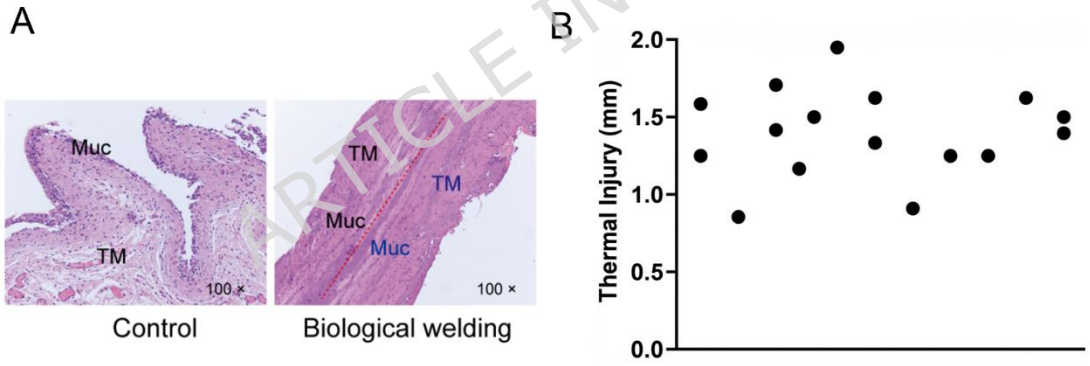

Figure 4 Hematoxylin and eosin (H&E) staining of bladder repair tissues after surgery. (A) Bladder tissue repaired by Biological welding under normal conditions;
(B) Scatter plot of the thermal injury range（0.8mm-2mm）. The red dashed line indicates the boundary between the bladder tissues on both sides of the wound.

Macroscopic Observation: Biological welding Promotes Fusion Tissue Recovery

The postoperative recovery process is a key indicator for evaluating the efficacy of surgical techniques. In the first 1–2 weeks after surgery, both groups of experimental subjects exhibited significant adhesion between the omentum and the bladder fusion site, with local tissue thickening, good wound healing, scar formation, and dilation and

thickening of surrounding blood vessels. The bladder was well-distended, presenting a regular sac-like shape (Figures 5A, C). In the control group, adhesion between the omentum and bladder was more pronounced than in the biological welding group. As the recovery time extended to 4 weeks, adhesion between the omentum and bladder anastomosis site decreased in both groups, with significantly less adhesion observed in the biological welding group. By 8 weeks postoperatively, partial adhesion of the omental tissue at the bladder suture site remained in the control group, but without vascular dilation or thickening; in contrast, adhesion in the biological welding group had almost completely resolved. At 12 weeks, no significant differences were observed in the normal adhesion of the bladder to the omentum between the two groups. The anastomotic sites showed no significant thickening, no vascular proliferation, good wound healing, and a well-distended bladder with a regular sac-like shape.

From an intravesical perspective, within the first 2 weeks postoperatively, both groups exhibited significant local mucosal edema at the bladder fusion site, with surrounding vascular dilation and thickening. Particularly in the control group, local congestion and thickening were prominent, with marked mucosal edema and pale coloration (Fig. 5B). In contrast, the biological welding group showed good healing of the bladder fusion site with minimal scar formation (Fig. 5C). As the healing time increased, edema in the biological welding group resolved more rapidly, with no signs of edema by week 8, closely resembling normal bladder mucosa. In the control group, mild edema and duller mucosal coloration persisted at the fusion site. At 12 weeks postoperatively, neither group exhibited diverticula or foreign bodies on the bladder wall. The biological welding group showed excellent healing of the bladder wall, with intact and rosy mucosa, no scar contracture, no trabecular proliferation, and no ulcers, indicating good wound repair. The control group also showed good healing, but with slightly reddish and swollen mucosa and mild local contracture, indicating a less favorable recovery compared to the biological welding group. These results demonstrate that, macroscopically, Biological welding promotes recovery of fusion tissues and reduces complications compared to traditional suturing techniques.

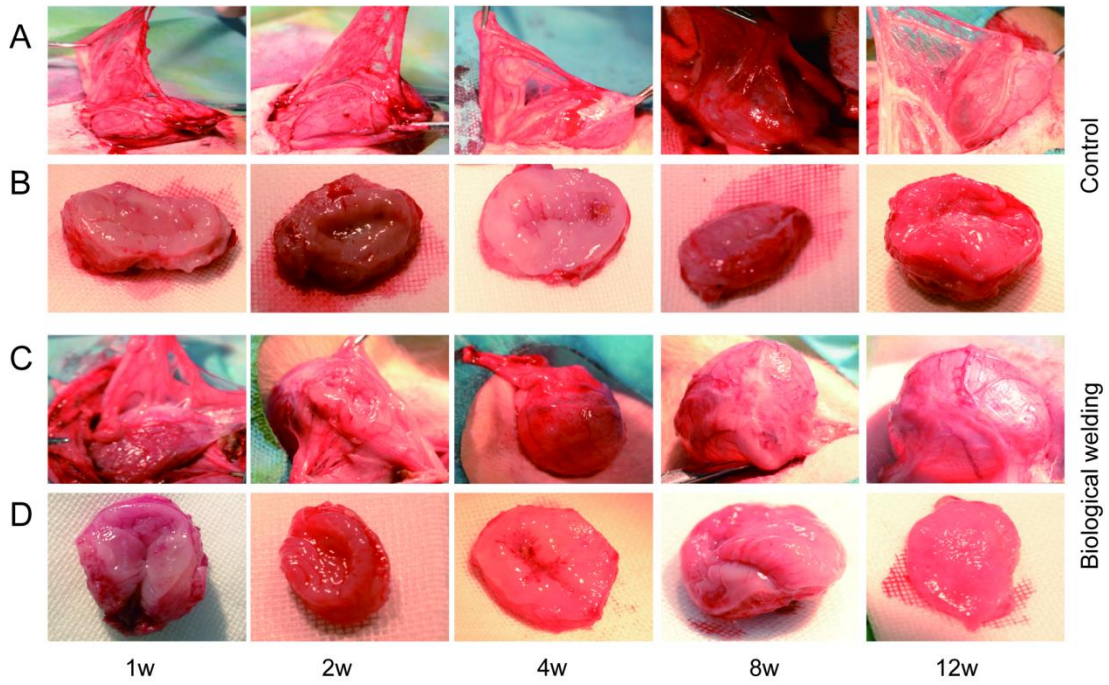

Figure 5 Recovery process of bladder tissues. (A) Representative images of the external surface of the bladder in the control group at different time points; (B) Representative images of the internal surface of the bladder in the control group at different time points; (C) Representative images of the external surface of the bladder in the biological welding group at different time points; (D) Representative images of the internal surface of the bladder in the biological welding group at different time points.

Histopathological and Raman spectroscopy Analysis: Biological welding Accelerates Fusion Tissue Recovery

Histopathological changes in postoperative tissues are important indicators for evaluating the effectiveness of new surgical methods. In this study, bladder repair tissue samples were collected at 1, 2, 4, 8, and 12 weeks postoperatively and subjected to hematoxylin and eosin (H&E) staining and histopathological analysis to assess the recovery outcomes. The results showed that in the control group, the wound tissues on both sides began to fuse at 1 week postoperatively, but the fusion area was not tightly integrated, with gaps present and significant inflammatory infiltration (Fig. 6). In contrast, the biological welding group exhibited a tighter fusion state in the welded area, with newly formed blood vessels observed at the edges of the welded region and mild

inflammatory infiltration, despite the presence of partially degenerated muscle fibers with disordered orientation that had not been fully absorbed (Fig. 6).

At 2 weeks postoperatively, the control group achieved tight closure of the wound fusion, with abundant fibroblasts and neovascularization in the repair area, accompanied by inflammatory cell infiltration. In comparison, the biological welding group showed that the partially degenerated muscle fibers had been largely absorbed, with a large number of newly generated fibroblasts and rich neovascularization, but with less prominent inflammatory cell infiltration than in the control group (Fig. 6). At 4 weeks postoperatively, undegraded sutures were still visible in the control group, with relatively loose organization of the newly formed muscle layer. In contrast, the biological welding group exhibited tightly arranged newly formed fibroblasts in the welded area, although their orientation was not yet fully organized (Fig. 6). At 8 weeks postoperatively, undegraded sutures remained visible in the control group. In contrast, the boundaries of the repair fusion area in the biological welding group became indistinct, with relatively ordered orientation of the newly formed muscle fibers and no significant differences from the surrounding tissues (Fig. 6). At 12 weeks postoperatively, no significant differences in the healing process were observed between the two groups, both showing good healing status with distinct layers of bladder tissue structure (Fig. 6). However, the newly formed tissue structure in the biological welding group was more compact than that in the control group. The above results indicate that, in terms of histopathology, biological welding can accelerate the recovery of fusion tissues compared to traditional suturing techniques.

Further Raman imaging was performed on four fused bladder tissue samples by analyzing spectra acquired from the welded region at 0 days post-welding (Figure 6A, 0-day welding arrowhead), with particular emphasis on collagen structure–related bands, including the amide I region (1600–1690 cm^{-1}; peptide C=O stretching) and collagen/protein-associated signals around 1300–1320 cm^{-1}[21,22]. The spectra exhibited characteristic peaks at 1664 cm^{-1} (amide I), 1313 cm^{-1} (a collagen-related band within 1200–1360 cm^{-1}, often associated with proline/hydroxyproline and CH_2

twisting/wagging), and 1450 cm^{-1} (CH_2 bending, commonly used for normalization). Compared with the control group, the welding group showed increased intensities at 1313, 1450, and 1664 cm^{-1}, suggesting early enrichment of collagen/protein components accompanied by molecular remodeling.

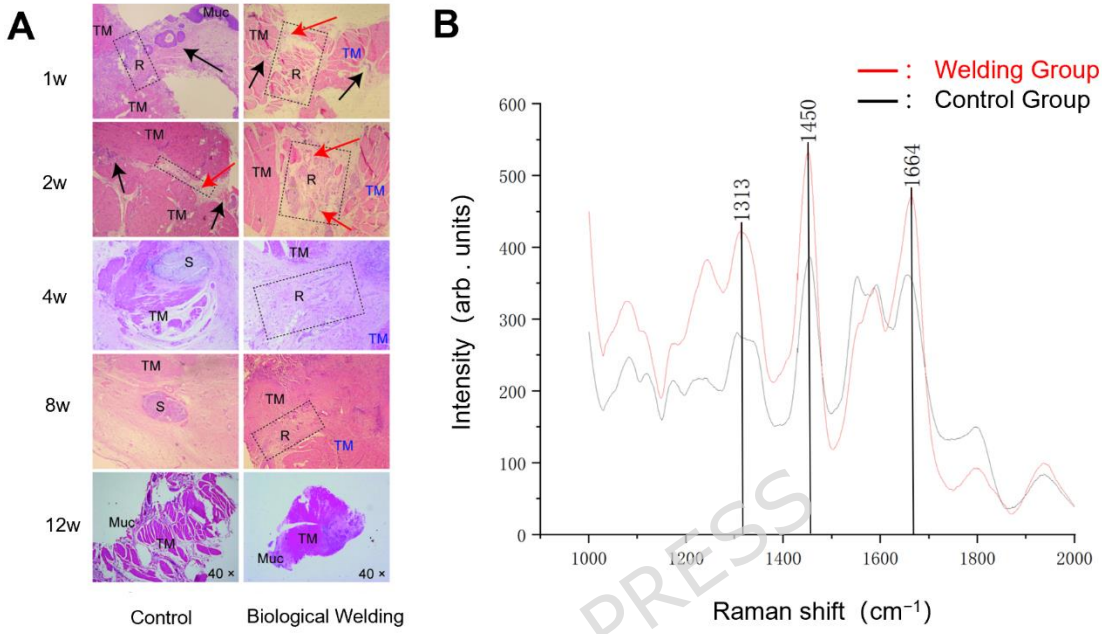

Figure 6

(A) Hematoxylin and eosin (H&E) staining of bladder repair tissues at different stages of recovery. Black arrows indicate inflammatory infiltration, and red arrows indicate blood vessels. Muc: Mucosal layer; TM: Muscular layer; S: Suture line; R: Tissue repair fusion area, i.e., the welded or sutured area.

(B) Raman Micro-Spectroscopy Results

Biological welding Mediates Limited Differential Gene Expression

To explore the molecular mechanisms underlying Biological welding in bladder tissue repair provides a theoretical basis for its clinical application. In this study, we collected bladder tissue samples from normal bladders and from bladders repaired at 1, 4, and 12 weeks postoperatively. Transcriptome sequencing was used to analyze the differences in gene expression among these samples. The results showed that at 1 week postoperatively, the biological welding group exhibited a greater number of differentially expressed genes compared with normal bladder tissue. At 4 weeks postoperatively, the number of differentially expressed genes in the biological welding group was similar to that in the control group. Notably, at 12 weeks postoperatively, the number of differentially expressed genes in the biological welding group was even

lower than that in the control group (Fig. 7). These findings suggest that although Biological welding has a more pronounced effect on gene expression in the short term after surgery, the duration of abnormal expression is shorter. This may indicate that Biological welding has the potential to promote rapid tissue repair.

These research results indicate that although the impact of biological welding on gene expression is more significant in the short term after surgery, the shorter duration of abnormal expression suggests that the immune response is limited and is consistent with the resolved immune/inflammatory response. This may imply that biological welding has the potential to promote rapid tissue repair.

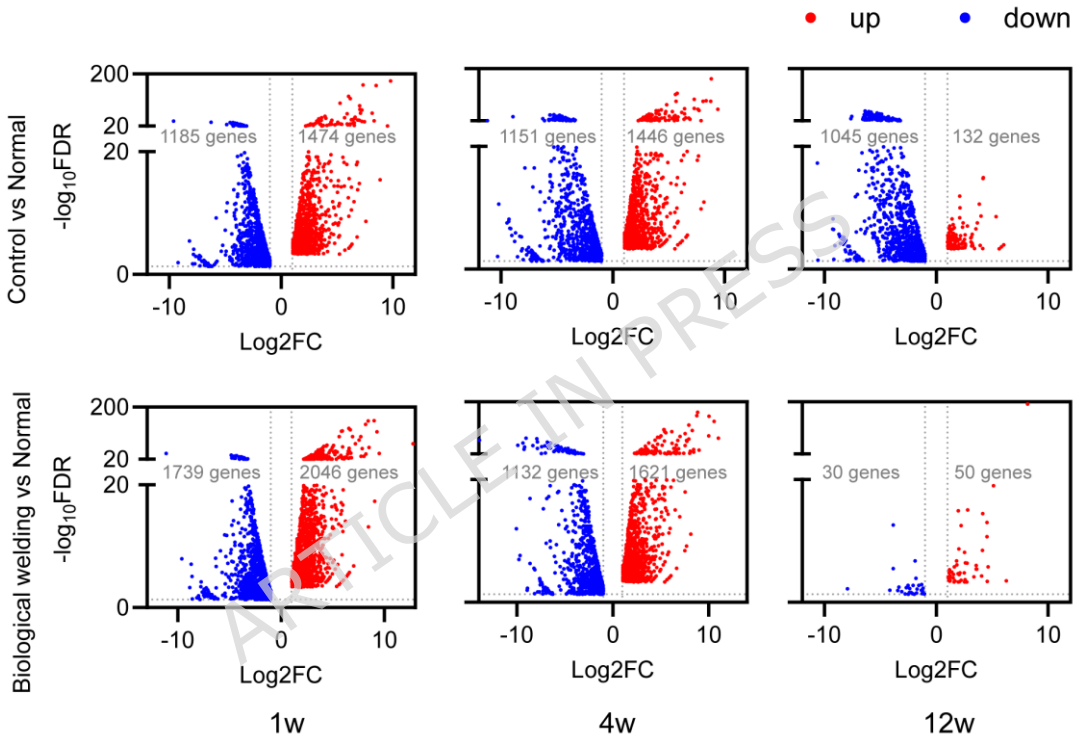

Figure 7 Volcano plot of differentially expressed genes in bladder repair tissues from transcriptome sequencing analysis.

Further analysis of the differentially expressed genes revealed that, compared with normal bladder tissue, the control group exhibited significant upregulation of 31 genes (padj < 0.05) and downregulation of 62 genes at 1, 4, and 12 weeks postoperatively (Fig. 8) (padj < 0.05). Similarly, in the biological welding group, 24 genes were significantly upregulated and 7 genes were significantly downregulated at different stages of recovery (padj < 0.05). In-depth analysis of these shared differentially

expressed genes showed that ADAM12, C1QTNF3, CHI3L1, CXCL14, GREM1, PTGFR, SFRP2, SPON1, and WT1 were significantly upregulated in both the control and biological welding groups (padj < 0.05), while CCR10 was significantly downregulated in both groups (padj < 0.05) (Fig. 8). These findings indicate that, at the level of gene expression, Biological welding shares commonalities with traditional suturing techniques in bladder repair but also exhibits specific differences.

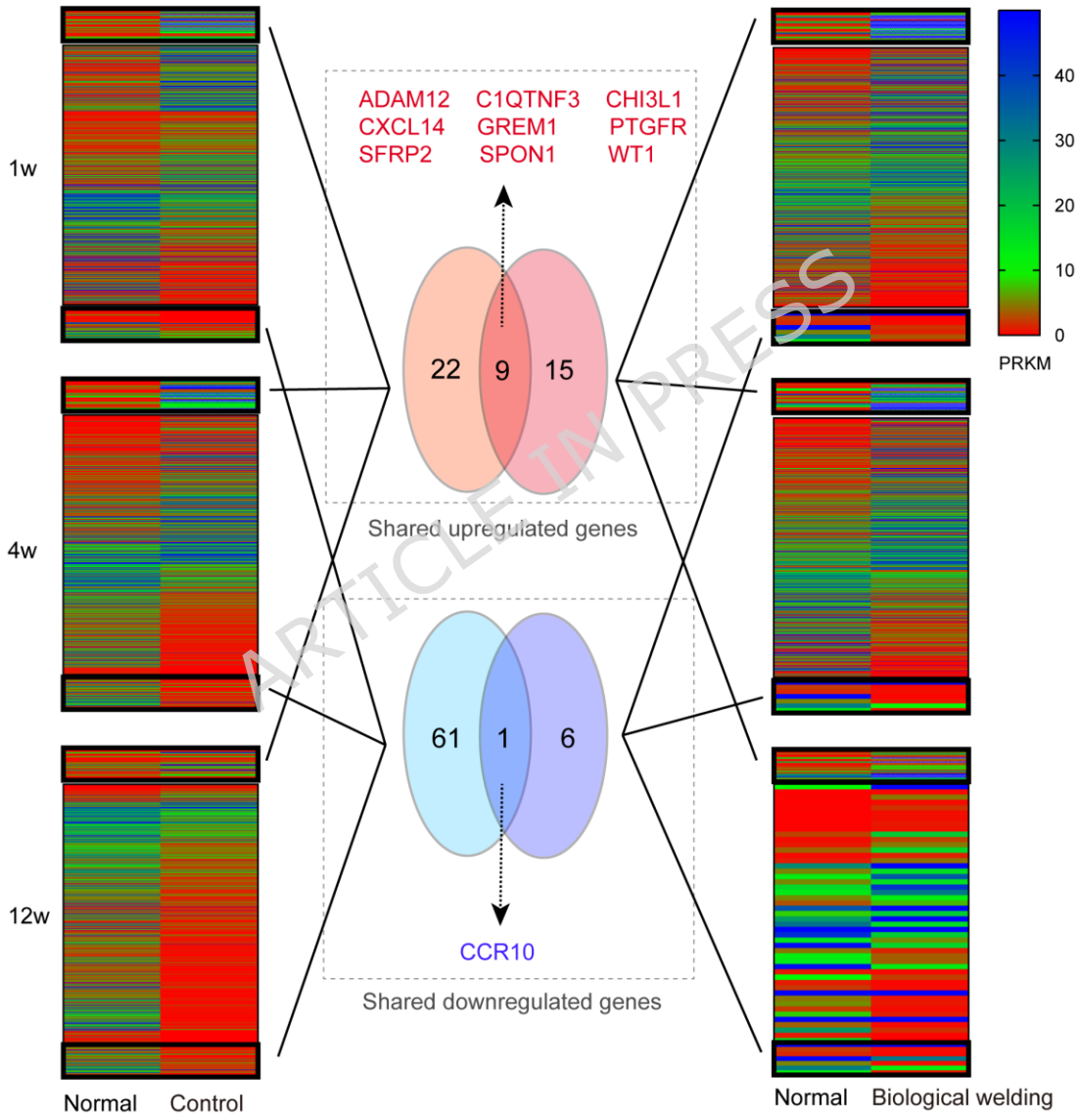

Figure 8 Analysis of differentially expressed genes in bladder repair tissues from transcriptome sequencing.

Biological welding Mediates a Limited Number of GO Terms in Bladder Repair

Annotation of differentially expressed genes with Gene Ontology (GO) terms helps to elucidate the molecular mechanisms underlying bladder repair. Our study found that, in the first 4 weeks postoperatively, a total of 13 GO terms were significantly enriched in both the biological welding and control groups, with the term “protein binding” having the highest number of enriched genes (Fig. 9A). This indicates that these GO terms, especially “protein binding,” play fundamental roles in the process of bladder repair.

Due to the reduced number of differentially expressed genes in the biological welding group at 12 weeks postoperatively compared to the normal control group, no significant enrichment of GO terms was observed (padj > 0.05). However, in the biological welding group at 1 and 4 weeks, as well as in the control group at 1, 4, and 12 weeks, GO terms related to immune response, such as “immune system process” and “GO:0006955,” were significantly enriched (padj < 0.05) (Fig. 9B). These findings suggest that the shared GO terms may play a key role in bladder repair, and the immune response induced by Biological welding may resolve earlier than that in the control group.

In the differential analysis of GO terms, 13 unique GO terms were involved in bladder repair in the control group during the first 12 weeks of recovery, while the biological welding group had only 4 unique GO terms (Fig. 9B). These results indicate that Biological welding mediates fewer GO terms in bladder repair compared to traditional suturing techniques.

Biological welding Mediates a Limited Number of KEGG Pathways in Bladder Repair

During the KEGG pathway enrichment analysis, we observed that the control group had a total of 24 significantly enriched KEGG pathways across different stages of recovery (padj < 0.05). Specifically, 1, 9, and 14 KEGG pathways were involved in bladder repair at 1, 4, and 12 weeks postoperatively, respectively (Fig. 10 A). In contrast, the biological welding group had a total of 14 significantly enriched pathways (padj < 0.05), with 5, 7, and 2 KEGG pathways involved at 1, 4, and 12 weeks postoperatively, respectively. These findings indicate that Biological welding activates only a limited number of KEGG pathways during bladder repair.

Further in-depth analysis of the KEGG pathways revealed that the pathway cfa05144 (malaria) was significantly enriched only in the biological welding group

across different stages of recovery, suggesting that cfa05144 may play a key role in bladder repair mediated by Biological welding. The cfa05144 pathway comprises 50 genes, and further analysis showed that 29, 27, and 4 differentially expressed genes were enriched in this pathway at 1, 4, and 12 weeks postoperatively, respectively. These differentially expressed genes appear to play a crucial role in this pathway. Notably, three differentially expressed genes (IL1B, LOC100855558, and LOC100855540) were consistently enriched throughout the entire time span of the repair process (Fig. 10 B). Therefore, we speculate that these genes may play a key role in the signal activation process of bladder repair mediated by Biological welding.

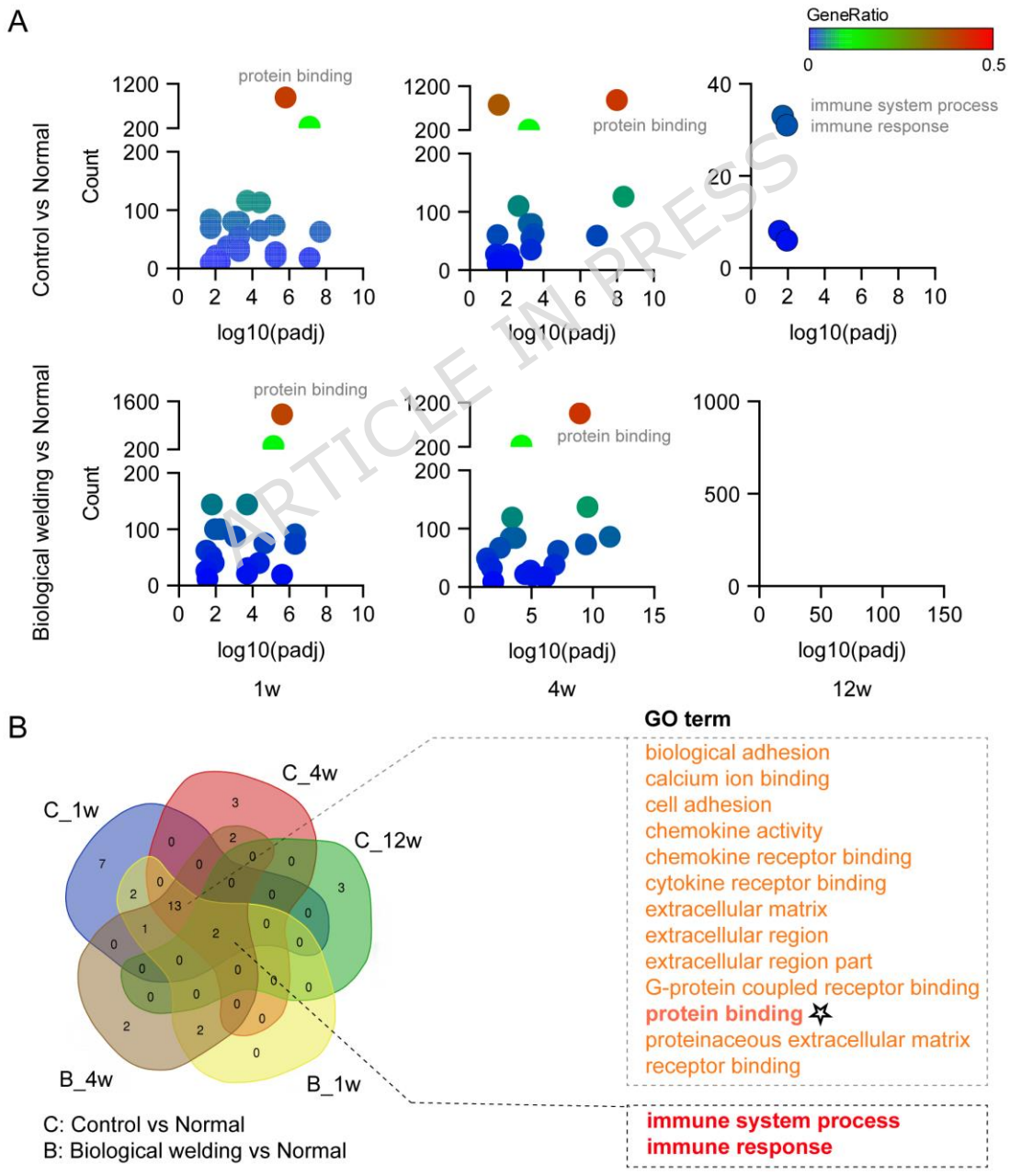

Figure 9 GO term annotation and analysis of differentially expressed genes in bladder repair tissues from transcriptome sequencing. (A) GO term annotation; (B) Analysis of shared GO terms enriched in differentially expressed genes between the two groups of bladder repair tissues.

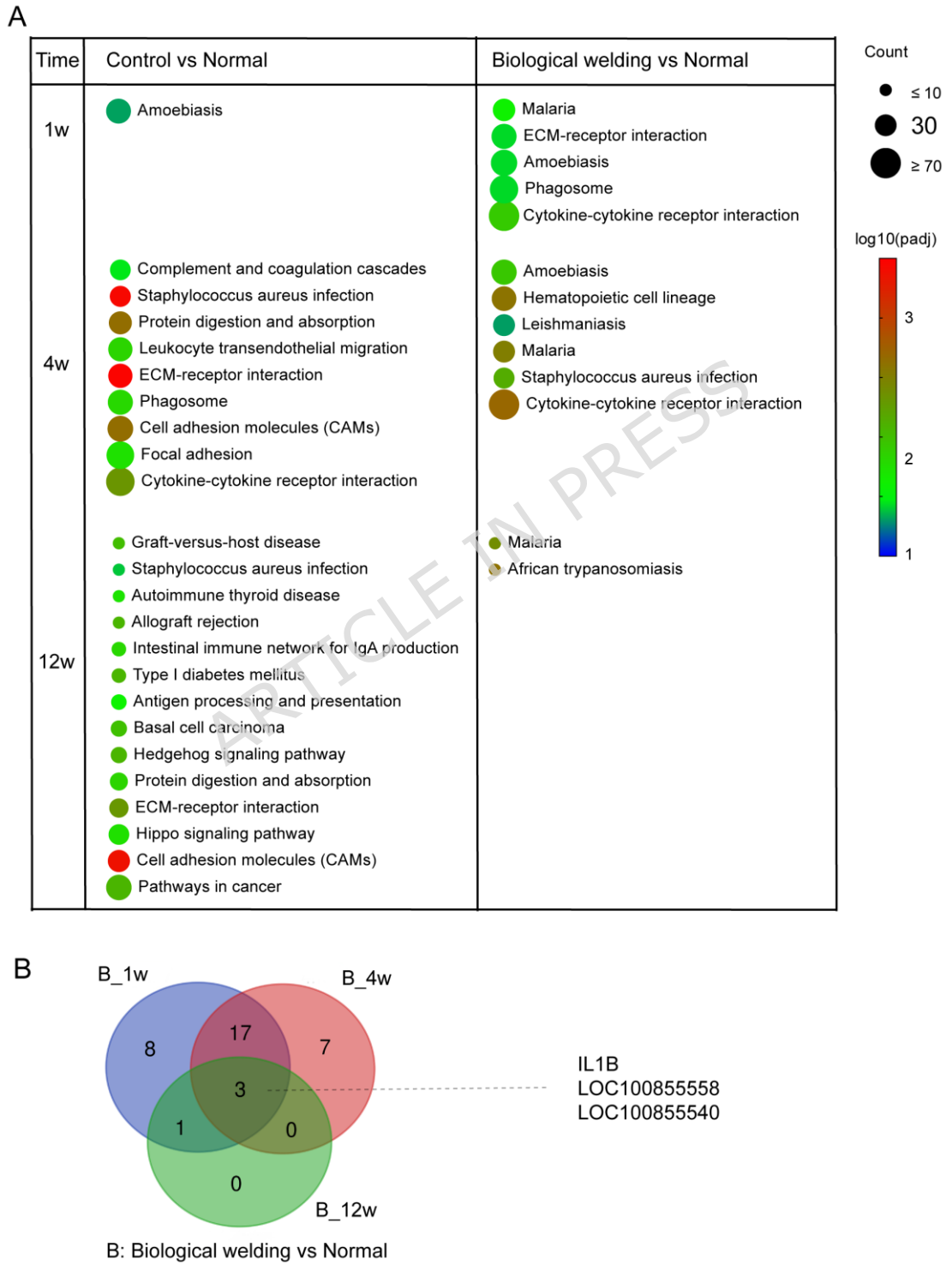

Figure 10 KEGG pathway annotation and analysis of differentially expressed genes in

the bladder repair tissue transcriptome sequencing. (A) KEGG pathway annotation; (B) Analysis of differentially expressed genes in the malaria signaling pathway[23].

Discussion

Biological welding, as an emerging surgical technique, has demonstrated significant potential in various soft tissue repair surgeries in recent years[15,19,20,24]. Its integration of cutting, hemostasis, and tissue fusion functions offers a more efficient and safer alternative for surgical procedures[17]. In the field of bladder repair, although traditional suture techniques are widely used, postoperative complications such as bleeding, infection, and urine leakage remain common[25-28]. This study systematically evaluated the application effects of Biological welding in bladder repair through animal experiments and compared it with traditional suture techniques, initially revealing its unique advantages in surgical safety, recovery speed, and repair mechanisms.

One of the core advantages of Biological welding is its significant enhancement of surgical safety. Compared with traditional suturing techniques, Biological welding achieves rapid tissue fusion through high-frequency currents, thereby reducing surgical time and intraoperative blood loss. This advantage has been consistently confirmed in multiple studies[18,19]. For example, in our study on the application of biological welding in circumcision, we found that the surgical time was reduced by approximately 90%, with virtually no bleeding[20].In the present study, the application of biological welding technology for bladder repair resulted in a 70.99% reduction in surgical time and a 79.02% decrease in intraoperative blood loss. In the control group, the surgical time exceeded 1 hour, referring to the entire process from laparotomy to complete abdominal cavity closure, not just the time for bladder suture. Moreover, using the full - thickness interrupted suture method to suture a 4 - to 8 - centimeter bladder incision at one time takes a relatively long time. Exceeding 1 hour indicates meticulous operations were carried out to ensure no. leakage In contrast, the welding operation has fewer steps, thus saving more time. Regarding blood loss, the longer the total time spent on hemostasis and suture, the greater the possibility of increased blood loss in the suture group. Additionally, the high - frequency energy used during the welding process has a hemostatic effect on small blood vessels, which may be one of the reasons for the reduced blood loss in the welding group. This is why the biological welding technique has significant advantages in surgical time and duration.

Moreover, Biological welding also excels in reducing postoperative complications. Postoperative inflammatory response is an important factor that affects surgical safety and the recovery process. Our study found that Biological welding significantly reduces postoperative inflammatory response, which is consistent with previous research findings[17,29,30]. For example, Liu et al. found in their study on the application of biological welding technology in intestinal repair that the M1 macrophages in the biological welding group peaked in the early postoperative period, while the M2 macrophages significantly increased in the mid-term postoperatively[29]. This ability to reduce postoperative inflammatory response may be attributed to the fact that Biological welding causes less mechanical damage to tissues, and the thermal effect of high-frequency currents can effectively seal blood vessels and lymphatics, thereby reducing the release of inflammatory mediators.

The potential of Biological welding to accelerate recovery is another significant advantage. Compared with traditional suturing techniques, Biological welding significantly shortens the recovery time by promoting rapid tissue fusion and reducing postoperative inflammatory responses. In this study, the bladder tissue in the biological welding group exhibited good healing status in the early postoperative period, with fewer complications. In the clinical study of vascular welding by Serhiy et al., it was demonstrated that biological welding reduced the hospital stay by 72.92%, and significantly decreased the incidence of side effects and complications[31]. Moreover, the 3-0 absorbable polyglycolic acid suture used in the control group produces a foreign body reaction during the absorption process. This may also be the reason why the degree of inflammatory cell infiltration observed in the suture group is higher than that in the welding group, because no foreign bodies are left in the welding group.

Moreover, Biological welding also demonstrates a significant advantage in reducing postoperative hematuria. Hematuria is one of the common complications following bladder repair surgery and may affect the recovery process of patients. In this study, the number of red blood cells in urine was significantly lower in the biological welding group than in the traditional suturing group, with some animals showing normal urine as early as the immediate postoperative period. This finding is similar to that of Kumar et al., who reported that Biological welding significantly reduces the incidence of postoperative hematuria in urological surgeries. The ability of Biological welding to reduce postoperative hematuria may be attributed to its minimal damage to the bladder mucosa and more effective sealing of blood vessels, thereby reducing

postoperative bleeding.

The unique advantages of Biological welding in bladder repair are not only reflected in surgical safety and recovery speed but also realized through its distinct mechanisms at the tissue and molecular levels. Biological welding can direct cell migration and fusion, thereby promoting rapid tissue healing, through the action of high-frequency currents. In this study, pathological analysis showed that the bladder tissue in the biological welding group exhibited good fusion status in the early postoperative period, with no significant inflammatory response. This cell migration phenomenon may be related to the biophysical effects of high-frequency currents, which can promote rapid tissue healing. In addition, Biological welding also shows significant advantages in reducing postoperative tissue adhesion. Compared with traditional suturing techniques, the biological welding group had less adhesion between the omentum and the bladder fusion site, which almost completely disappeared by 4 weeks postoperatively. This ability to reduce postoperative adhesion may be due to the use of Biological welding, which can significantly reduce bleeding at the wound site and more effectively promote rapid tissue healing.

Transcriptomic sequencing analysis preliminarily explored the molecular mechanisms of Biological welding in bladder repair. Compared with traditional suturing techniques, Biological welding exhibited more differentially expressed genes in the early postoperative period, but the duration of abnormal expression was shorter. This indicates that Biological welding can rapidly initiate the tissue repair process and restore normal gene expression patterns in a short time. Further analysis revealed that Biological welding significantly enriched GO terms and KEGG pathways related to immune responses at 1 and 4 weeks postoperatively. These results suggest that bio-welding may promote rapid tissue repair by seamless healing and activating a limited number of immune response-related genes and signaling pathways. Additionally, the number of differentially expressed genes in the biological welding group at 12 weeks postoperatively was significantly reduced, indicating that its impact on gene expression is transient and further confirming its potential to promote rapid tissue repair.

Compared with traditional suture techniques, biological welding technology exhibits higher efficiency and precision in the molecular repair mechanisms. For instance, in the study conducted by Liu's team, the intestinal anastomosis tissues treated with biological welding technology demonstrated significant macrophage infiltration and functional polarization[29]. The M1 macrophages (pro-inflammatory phenotype)

peaked in the early postoperative period, while the M2 macrophages (anti-inflammatory and tissue repair phenotype) significantly increased in the mid-term postoperatively. This precise regulation of immune cells is likely one of the important reasons why biological welding technology shows significant advantages in tissue repair.

Limitations

Several limitations of our study warrant consideration. First, the bladder rupture model created via a clean cystotomy in healthy, well-perfused tissue does not fully replicate the complex pathophysiology of traumatic bladder rupture seen in a clinical setting, which often involves contused, edematous, and ischemic tissue. Future studies should evaluate the efficacy of biological welding in more clinically realistic trauma models. Second, while our results showed no urine leakage and burst pressures exceeding physiological levels, we did not conduct urodynamic tests to assess bladder compliance. Therefore, it remains unclear whether the welded scar tissue could form a non-compliant segment that might affect long-term bladder function. Future research should include comprehensive urodynamic assessments. Third, although histopathological analysis revealed only mild thermal injury that was acceptable given the favorable healing outcomes, we did not perform a quantitative measurement of the lateral thermal spread. Defining the precise safety margin for the surrounding healthy detrusor muscle is an important area for further investigation. Fourth, regarding potential pediatric applications, it is unknown whether the welded tissue can adequately expand to accommodate bladder growth over time. While welding avoids the use of non-growing synthetic materials, long-term studies in growing animal models are required to assess this crucial aspect. Fifth, our discussion regarding the potential for electrical stimulation to promote umbrella cell migration is purely speculative and serves as a hypothesis for future investigation rather than a confirmed finding of this study（Supplementary Materials）. Long-term studies with larger sample sizes are necessary to fully evaluate the durability of the repair, late-onset complications, and the potential for bladder stone formation at the welding site.

Conclusion

This study is the first to evaluate the application of biological welding in bladder rupture repair, demonstrating that it significantly outperforms traditional suturing techniques in terms of surgical efficiency, blood loss reduction, and postoperative recovery. Histological and Raman spectroscopy analysis revealed that biological welding promotes collagen crosslinking and orderly arrangement, accelerating tissue healing and reducing postoperative adhesions. Despite mild thermal damage due to temperature increase, biological welding shows great potential for clinical use in bladder repair, offering a new solution for soft tissue repair in the future.

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Author's Contribution

Conception and design: Zhongyi Sun, Fanchun Zeng. Collection data: Fanchun Zeng, Fengwen Fu, Quanfu Cao，Minggan Guo，Yuan Chen. Data analysis and interpretation: Zhongyi Sun and Fanchun Zeng. Manuscript preparation: Fanchun Zeng, Revision of the manuscript: Zhongyi Sun. Manuscript: All authors.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Zenodo repository, https://doi.org/10.5281/zenodo.18255296.

Declarations

Ethics

The experiments adhered to the guidelines for the care and use of laboratory animals and were approved by the Animal Ethics Committee of the Third Military Medical University Daping Hospital (Animal Ethics Approval ： Medical Research and Review (2015) No. 53).

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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