We sincerely thank you for your thorough and insightful comments, which have significantly helped us improve the quality of our manuscript. We have carefully revised the manuscript according to your suggestions. Point-by-point responses are as follows:

Reviewer #1(Remarks to the Author):

Point 1: The phrase "ESD is quite complicated to perform and requires a high level of skill, and also may lead to various..." is proposed to be replaced by "ESD is a technically demanding procedure associated with significant complications, such as hemorrhage and perforation." Also, "spraying tissue adhesive to hemostasis" should be corrected to "spraying tissue adhesive for hemostasis".

Response: We fully agree with your suggestion. We have revised the sentence accordingly in the introduction section. Additionally, we have corrected the prepositional phrase in the same section. **Revised text:** "ESD is a technically demanding procedure associated with significant complications, such as hemorrhage and perforation... spraying tissue adhesive for hemostasis."

Point 2: "A 59-year-old male patient referred to our hospital..." should be replaced with "was referred to"; "computed tomography (CT) of the abdomen did not reveal abnormal" should be replaced with "did not reveal any abnormalities."

Response: We apologize for these grammatical oversights. We have corrected both sentences in the case presentation section. **Revised text:** "A 59-year-old male patient was referred to our hospital..." and "...did not reveal any abnormalities."

Point 3: The term "gastric horn" is unusual. The term "gastric angulus" is suggested.

Response: Thank you for pointing out this terminological inaccuracy. We have replaced "gastric horn" with the standard anatomical term "gastric angulus" in the manuscript.

Point 4: A more extensive description of the procedure should be provided. The type of tissue adhesive (e.g., N-butyl-2-cyanoacrylate) and the method of administration (e.g., via a special catheter) should be mentioned. More specific information should be provided about the material used (e.g., which formulation of cyanoacrylate adhesive? What protocol?).

Response: We appreciate this important suggestion. To enhance the reproducibility of our technique, We have added a video detailing the procedure in the treatment section. Specifically, we have added the following information in the video:

Material: We used N-butyl-2-cyanoacrylate (Kangpaite®, Beijing Compont Medical Devices Co., Ltd., Beijing, China).

Administration method: The adhesive was sprayed via a specialized endoscopic spray catheter.

Protocol: In the spray application of tissue adhesive, the spraying catheter is first pre-flushed with 50% glucose solution. The catheter was then inserted through the endoscopic working channel and advanced at least 1 cm beyond the tip of the endoscope to prevent the adhesive from contaminating the lens. Subsequently, 0.5 mL of tissue adhesive was mixed with 3 mL of 50% glucose solution, and the mixture was slowly injected into the spray catheter using a syringe for application onto the wound surface. The spray was delivered in a gravity-dependent order, from the higher to the lower portion of the wound, ensuring complete coverage of the entire defect. The dosage was considered

adequate when active bleeding ceased completely and a firm adhesive cast was observed covering the bleeding site, and repeated spraying of the glue-glucose mixture can be performed as needed.

Point 5: "we did observe" should be changed to "we observed".
Response: We have corrected this emphatic tense to a simple past tense in the treatment section.
Revised text: "we observed...".

Point 6: The sentence "menacing the patient's life safety" should be replaced with "posing a significant clinical challenge" or "potentially life-threatening"; "α-cyanoacrylic acid butyl enzyme" should be replaced with "butyl-cyanoacrylate".
Response: We agree with your precise wording. We have revised the discussion section accordingly. The phrase has been changed to "potentially life-threatening" , and we have corrected the chemical name to "butyl-cyanoacrylate".

Point 7: The comparative advantage of glue spraying over hemostatic sprays (TC-325/Hemospray) should be defined more clearly. Please explain why glue is superior or in which cases it is a better solution. Please comment on why this method is superior to other modern techniques.
Response: We greatly appreciate this constructive suggestion. In accordance with your request, we have added a comparison between tissue adhesive spraying and hemostatic powders (such as TC-325/Hemospray) in the discussion section.
Specifically, we have incorporated the following key points:
Both tissue adhesives and hemostatic powders belong to the category of topical hemostatic agents, which serve as important supplements to conventional endoscopic modalities (injection, clipping, and thermal coagulation) due to their ease of use, non-contact application, and broad coverage, particularly for refractory or diffuse bleeding(*Endoscopy. 2009;41 Suppl 2:E27-8; Endoscopy. 2011;43 Suppl 2 UCTN:E227-8; Gastrointest Endosc. 2013 Sep;78(3):536-9; Gastrointest Endosc. 2025 Jan;101(1):36-44.*). However, we highlighted that hemostatic powders are delivered via gas-driven propulsion, which may cause barotrauma, catheter looping, and impaired visualization during treatment. Moreover, powder particles tend to clog the catheter upon contact with mucus, potentially interfering with the procedure. In contrast, spraying tissue adhesive is simpler to perform, does not involve barotrauma, and maintains good visualization throughout treatment, making it a more favorable option in certain challenging scenarios.(*Gastrointest Endosc. 2025 Jan;101(1):36-44.*) Nevertheless, we also noted that caution should be exercised to prevent glue from obstructing the endoscope's working channel.

Reviewer #2(Remarks to the Author):

Point 1 (Introduction): "Hemorrhage during ESD procedures is almost inevitable, particularly in large-size lesions with large mucosal defects, where traditional methods such as titanium clips and nylon strings do not work well." The description is inappropriate. According to Ref 5, "In particular, in cases of ESD, coagulation of bleeding vessels using hemostatic forceps, which does not interfere with subsequent resection, is the first-choice technique." Coagulation of visible bleeding vessels is preferred during ESD procedure, rather than other methods.
Response: We thank the reviewer for this important correction. Our previous expression was

indeed inaccurate; thermal coagulation of bleeding vessels during the procedure is the first-line choice. What we intended to convey in the manuscript is that, in the context of large ESD defects, titanium clips and nylon endoscopic sutures are limited in achieving wound closure, which may increase the risk of postoperative bleeding. Accordingly, in our manuscript we have revised the original sentence from "where traditional methods such as titanium clips and nylon strings do not work well" to " wherein conventional modalities such as titanium clips and endoloop ligation have limited efficacy for hemostasis and resection defect closure".

Point 2 (Case presentation): According the manuscript, endoscopic tissue adhesive was applied to stop bleeding after heat coagulation. Please provide more details. A short video clip is suggested. Firstly, the reason for choosing endoscopic tissue adhesive but not hemostatic powder. Following the package insert, endoscopic tissue adhesive should be applied to esophagogastric variceal bleeding. Secondly, the spraying sequence, the usage amount, how to judge whether the dosage was sufficient, and how to avoid any blockage in the endoscopic channel. Thirdly, how to testify endoscopic tissue adhesive rather than PPI drugs could prevent delayed bleeding.

Response: We greatly appreciate these constructive suggestions. We have substantially expanded the manuscript with the following details:

(a) Reason for choosing tissue adhesive over hemostatic powder : Both tissue adhesives and hemostatic powders belong to the category of topical hemostatic agents, which serve as important supplements to conventional endoscopic modalities (injection, clipping, and thermal coagulation) due to their ease of use, non-contact application, and broad coverage, particularly for refractory or diffuse bleeding(*Endoscopy. 2009;41 Suppl 2:E27-8; Endoscopy. 2011;43 Suppl 2 UCTN:E227-8; Cyanoacrylate spray for treatment of difficult-to-control GI bleeding; Gastrointest Endosc. 2025 Jan;101(1):36-44.*). However, we highlighted that hemostatic powders are delivered via gas-driven propulsion, which may cause barotrauma, catheter looping, and impaired visualization during treatment. Moreover, powder particles tend to clog the catheter upon contact with mucus, potentially interfering with the procedure. In contrast, spraying tissue adhesive is simpler to perform, does not involve barotrauma, and maintains good visualization throughout treatment, making it a more favorable option in certain challenging scenarios.(*Gastrointest Endosc. 2025 Jan;101(1):36-44.*) Nevertheless, we also noted that caution should be exercised to prevent glue from obstructing the endoscope's working channel.

(b) Spraying sequence, usage amount, dosage sufficiency, and blockage prevention: We produced a short video in our article to answer this question. We used N-butyl-2-cyanoacrylate (Kangpaite®, Beijing Compont Medical Devices Co., Ltd., Beijing, China).The adhesive was sprayed via a specialized endoscopic spray catheter. In the spray application of tissue adhesive, the spraying catheter is first pre-flushed with 50% glucose solution. The catheter was then inserted through the endoscopic working channel and advanced at least 1 cm beyond the tip of the endoscope to prevent the adhesive from contaminating the lens. Subsequently, 0.5 mL of tissue adhesive was mixed with 3 mL of 50% glucose solution, and the mixture was slowly injected into the spray catheter using a syringe for application onto the wound surface. The spray was delivered in a gravity-dependent order, from the higher to the lower portion of the wound, ensuring complete coverage of the entire defect. The dosage was considered adequate when active bleeding ceased completely and a firm adhesive cast was observed covering the

bleeding site, and repeated spraying of the glue-glucose mixture can be performed as needed.

(c) **How to testify endoscopic tissue adhesive rather than PPI drugs could prevent delayed bleeding:** We greatly appreciate the reviewer for raising this point regarding postoperative PPI therapy. Our previous manuscript did not describe this aspect clearly enough. In this case, we also administered PPI therapy after the ESD procedure to prevent postoperative bleeding, and we have now supplemented the manuscript with details on the postoperative PPI regimen.

(d) **A short video demonstrating endoscopic tissue adhesive spray treatment:** We have made a short video of tissue adhesive spray treatment to demonstrate the details of the procedure.

Point 6 (Discussion): There is one mistake. The main component of endoscopic tissue adhesive is should be "n-butyl α-cyanoacrylate ester", but not "α-cyanoacrylic acid butyl enzyme". Comparison endoscopic tissue adhesive with hemostatic powder is recommended.

Response: We thank the reviewer for catching this critical terminological error. We have corrected the chemical name throughout the manuscript from "α-cyanoacrylic acid butyl enzyme" to "butyl-cyanoacrylate" (also known as n-butyl α-cyanoacrylate ester). We appreciate the reviewer's recommendation to compare endoscopic tissue adhesive with hemostatic powder. As detailed in our response to Point 2 ("Reason for choosing tissue adhesive over hemostatic powder"), we have not only provided a thorough rationale but also added the comparative analysis to the appropriate section of the manuscript.

Point 7 (References): Please check the references using auto-analyser supported by Baishideng.

Response: We have carefully checked all references using the Baishideng auto-analyser as recommended-. All references have been verified for accuracy and formatted according to the journal's requirements. The reference list has been updated accordingly.

Reviewer #3(Remarks to the Author):

Point 1: The authors should compare sprayed tissue adhesive with established shielding techniques, particularly polyglycolic acid (PGA) sheets and fibrin glue. They should cite and discuss the relevant report published in World Journal of Gastroenterology in 2016 (World J Gastroenterol. 2016 Jul 14;22(26):5927-5935. doi: 10.3748/wjg.v22.i26.5927). This comparison would clarify whether the present method has advantages in simplicity, adhesion, cost, procedure time, or prevention of delayed bleeding.

Response: We greatly appreciate this important suggestion. As we have no experience with PGA sheet therapy, we lack sufficient data on its treatment costs and hemostatic efficacy. Based on your recommendation, we reviewed the relevant literature and learned that PGA sheets are mesh-like, flexible, and tensile high-molecular-weight polymers. Fibrin glue consists of fibrinogen and thrombin; when these two components are mixed, they form a highly adhesive gel that firmly secures the PGA sheet to the wound surface. "PGA sheets + fibrin glue" provides an important adjunctive measure for preventing post-ESD perforation and bleeding. To date, we have not found any literature comparing sprayed tissue adhesive with classic gastrointestinal hemostatic methods such as PGA sheets and hemostatic powder. However, in terms of operational procedure, we suggest that sprayed tissue adhesive is simpler to perform than "PGA sheets + fibrin glue". Finally, we have added a comparison between sprayed tissue adhesive and established covering techniques,

particularly PGA sheets combined with fibrin glue, in the discussion section. We have cited a relevant review by Kataoka et al., published in the *World Journal of Gastroenterology* in 2016.

Point 2: The authors should explain whether α-cyanoacrylate butyl ester has been used in other medical procedures. Examples such as vascular embolization, skin wound closure, treatment of gastrointestinal varices, and management of postoperative or traumatic bleeding would support the rationale for its gastrointestinal application and help readers assess its safety based on previous clinical experience.

Response: Thank you for your reminder. In the discussion section, we have added a paragraph addressing the established clinical applications of butyl-cyanoacrylate (also known as n-butyl α-cyanoacrylate ester, NBCA) in various medical fields: The hemostatic mechanism of spraying tissue adhesive relies on rapid cyanoacrylate polymerization upon contact with blood, forming a solid plug that occludes the target vessel and achieves hemostasis (*Radiographics,2026;46(5):e250122*). NBCA has been widely used for hemostasis in various settings, with previous reports covering portal vein embolization, cerebral vessel embolization, hemorrhagic trauma, and gastrointestinal bleeding. Available evidence indicates that NBCA hemostasis is non-inferior to conventional treatments, such as clipping, in terms of hemostatic efficacy (*Diagn Interv Imaging, 2021;102(7-8):479-487*).

Point 3: Possible adverse effects should be addressed. These may include local irritation, inflammation, delayed ulcer healing, foreign-body reaction, allergic reaction, infection, or difficulty in detecting recurrence during follow-up endoscopy. The authors should state whether adverse events occurred and describe how the adhesive amount, spraying distance, and target area were controlled to reduce risk.

Point 4: The manuscript should mention possible damage to endoscopic equipment. Because cyanoacrylate polymerizes rapidly after contact with fluid, it could clog the spray catheter, adhere to the endoscope tip, contaminate the working channel, or reduce visibility. Practical precautions, such as using a dedicated catheter and avoiding contact with the lens, should be described.

Response: As the replies to Point 3 and Point 4 contain overlapping aspects, we have consolidated our responses to both questions and present them together below:

We agree that this is a critical aspect of safety assessment. Tissue adhesives are primarily used for hemostasis in vascular interventional therapy and laparoscopic surgery. Currently, reports on their use as a topical spray for gastrointestinal bleeding are limited. After reviewing the relevant literature, we found that in vascular interventional procedures (including treatment of gastroesophageal varices) and laparoscopic surgery, potential adverse effects may include non-target vessel embolization, tissue ischemia, catheter lumen occlusion, abdominal pain, and intestinal obstruction.(*Radiographics.2026May;46(5):e250122;BMC Gastroenterol. 2019 Dec 21;19(1):224.*)

However, in the context of spray application of tissue adhesives, aside from the risk of luminal obstruction, no other treatment-related adverse effects have been reported. As noted in the case presentation, no specific complications—such as local irritation, inflammation, delayed ulcer healing, foreign-body reaction, allergic reaction, infection, or difficulty in detecting recurrence—were observed during the follow-up period. The patient recovered uneventfully.

In order to address the issue raised in Point 3 (specifically, 'how the adhesive amount, spraying distance, and target area were controlled to reduce risk') and the issue in Point 4, we have made a

short video of tissue adhesive spray treatment to demonstrate the details of the procedure.

Point 5: The authors should clarify the appropriate indications. Sprayed adhesive may be most useful for wide but superficial mucosal defects, whereas deep defects with exposed large vessels, muscular injury, or suspected perforation may require additional hemostatic methods, clipping, or surgical consultation. Defining these limitations would make the report more clinically useful.

Response: We greatly appreciate this constructive suggestion. In the conclusion section, we have added a clear delineation of the appropriate indications and limitations of sprayed tissue adhesive for post-ESD hemostasis. We propose that sprayed tissue adhesive is most suitable for wide but superficial mucosal defects where conventional clipping is technically challenging or insufficient, for diffuse oozing from large post-ESD ulcers, for bleeding from irregular or fibrotic ulcer bases where forceps coagulation or clipping may be ineffective, and for cases refractory to conventional hemostatic methods such as injection, clipping, or thermal coagulation. However, we emphasize that sprayed adhesive should not be used as a standalone treatment in certain high-risk scenarios, including deep defects with exposed large vessels (visible vessel or spurting bleeding), where hemostatic forceps coagulation or clipping remains the first-line treatment; muscular injury or suspected perforation, which may require additional closure methods such as endoscopic clipping, over-the-scope clips, or surgical consultation.