

ORIGINAL ARTICLE

Consensus of free flap complications: Using a nomenclature paradigm in microvascular head and neck reconstruction

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Abstract

Background: We aim to define a set of terms for common free flap complications with evidence-based descriptions.

Methods: Clinical consensus surveys were conducted among a panel of head and neck/reconstructive surgeons ($N = 11$). A content validity index for relevancy and clarity for each item was computed and adjusted for chance agreement (modified kappa, K). Items with $K < 0.74$ for relevancy (i.e., ratings of “good” or “fair”) were eliminated.

Results: Five out of nineteen terms scored $K < 0.74$. Eliminated terms included “vascular compromise”; “cellulitis”; “surgical site abscess”; “malocclusion”; and “non- or mal-union.” Terms that achieved consensus were “total/partial free flap failure”; “free flap takeback”; “arterial thrombosis”;

“venous thrombosis”; “revision of microvascular anastomosis”; “fistula”; “wound dehiscence”; “hematoma”; “seroma”; “partial skin graft failure”; “total skin graft failure”; “exposed hardware or bone”; and “hardware failure.”

Conclusion: Standardized reporting would encourage multi-institutional research collaboration, larger scale quality improvement initiatives, the ability to set risk-adjusted benchmarks, and enhance education and communication.

KEYWORDS

free flap complications, head and neck, microvascular reconstruction, outcomes, quality improvement

1 | INTRODUCTION

There are inherently different preoperative risk factors in head and neck oncologic patients when compared to general surgery patients and even general otolaryngology patients. Factors specific to the head and neck cancer population are not currently included in standard variables for commonly used outcome reporting databases such as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), or otolaryngology specific databases such as the American Academy of Otolaryngology—Head and Neck Surgery ENT Clinical Data Registry (Reg-ent), and the Creating Healthcare Excellence through Education and Research (CHEER) network.

Moreover, there is considerable variability and ambiguity regarding nomenclature for complications in head and neck reconstructive surgery, particularly for free tissue transfer. Several known adverse events in free flap reconstruction are not reported at all, including vessel anastomosis issues and postoperative bleeding events; both contribute to prolonged operative time and early reoperations leading to increased length of stay and subsequent serious complications.^{1–4} Lack of a unified language for describing and documenting these complications results in ambiguity and confusion when reporting outcomes, difficulty comparing research findings from different institutions, and poor communication between providers, patients, trainees, and colleagues.

As such, there is a need to develop a nomenclature paradigm to characterize free flap complications in microvascular head and neck reconstruction. Through consensus among a panel of experts in head and neck oncology and microvascular reconstruction, the authors aim to define a set of common free flap complications. We present a definition and evidence-based description for each of these terms. It is beyond the scope of this paper to define the diagnostic criteria or management options for each term in detail. Our goal is to facilitate

clarity in reporting free flap outcomes; improve communication among team members, patients, and interdisciplinary care teams; and promote collaboration in clinical research.

2 | METHODS

Clinical consensus surveys were conducted among a panel of head and neck and facial plastics and reconstructive surgeons (Steven B. Cannady, Steven B. Chinn, Tanya Fancy, Neal Futran, Matthew M. Hanasono, Carol M. Lewis, Brett A. Miles, Urjeet Patel, Jeremy D. Richmon, Mark K. Wax, Peirong Yu). The proposed terms were developed through a content validation process based on Lynn’s methodology.^{5–7} Emphasis was placed on defining and describing a set of terms that would appropriately capture the most common head and neck microvascular free flap complications. The terms included are intended to be clinically appropriate, promote consistency in identifying these events in medical records, aid in reporting research and outcomes, and serve as a tool for clinical education. The content validation procedure for the nomenclature paradigm presented herein was conducted in two stages: (a) Stage 1, Development and (b) Stage 2, Judgment and quantification.

2.1 | Stage 1: Development

An iterative literature review process was used (Leila J. Mady, Vusala Snyder, Chareeni Kurukulasuriya) to provide the theoretical framework for term selection, definitions, and supporting descriptions. An initial survey was distributed to panel members who were asked to agree or disagree with term definitions and provide critiques for suggested revisions based on their clinical experience. Based on the results of the literature reviews and expert comments, a second draft of terms was developed and redistributed to panel members.

2.2 | Stage 2: Judgment and quantification

In the second survey, panel members were asked to evaluate each term and supporting descriptions for relevance and clarity. Each item was scored on a 4-point scale (Table 1). In addition, experts could provide further comments on each item. A content validity index for relevancy and clarity of each item (I-CVI) was computed as the number of those judging the item as relevant or clear (rating 3 or 4) divided by the number of panel experts. The I-CVI conveys the proportion of agreement, measured between zero and one, on the relevancy or clarity of each item. For relevancy, a scale-level index (S-CVI) was also calculated to determine the proportion of total items judged content valid by averaging the I-CVIs.⁸ For calculating the S-CVI, the scale is first dichotomized by combining values 3, 4 (“relevant”) and 2, 1 (“not relevant”) for each item. Then the sum of I-CVIs is divided by the total number of items to yield the average S-CVI.⁹ Agreement of 80% or greater is recommended for new instruments.⁶

Additionally, a multirater kappa statistic was computed to adjust the I-CVI for chance agreement.^{9,10} The modified kappa (*K*) is a consensus index of inter-rater agreement among experts that indicates beyond chance that the item is relevant or clear. To calculate *K*, the probability of chance agreement (P_C) was first computed for each item by the following formula: $P_C = [N!/A! (N - A)!] \times 0.5^N$, where N = number of panel experts and A = number of panelists who agree that the item is relevant or clear. After calculating I-CVI for all survey items, *K* was computed by the following formula: $K = (I-CVI - P_C)/(1 - P_C)$. Evaluation criteria for *K* were considered excellent (above 0.74), good (between 0.60 and 0.74), and fair (between 0.40 and 0.59).¹¹ Items that achieved adjusted I-CVI (modified kappa) scores below 0.74 (i.e., *K* ratings of “good” or “fair”) for relevancy were eliminated from inclusion in the final set of terms.

3 | RESULTS

Terms, I-CVI scores for relevancy and clarity, and *K* are depicted in Table 2. Details regarding terms that were eliminated can be found in the Supporting Information. There was 85% agreement by consensus panel members for terms considered relevant as calculated by the S-CVI. Terms and their supporting descriptions which achieved consensus are detailed below.

3.1 | Consensus terms

1. (A) Total free flap failure—loss of (1) all muscle, skin, or bone in a muscle-only, cutaneous, or osseous flap,

TABLE 1 Content validity rating scale

Relevancy	Clarity
1 [not relevant]	1 [not clear]
2 [item need some revision]	2 [item need some revision]
3 [relevant but need minor revision]	3 [clear but need minor revision]
4 [very relevant]	4 [very clear]

Notes: Proposed terms were developed through a content validation process based on Lynn's methodology.^{11–13} Panel members were asked to score each term and supporting descriptions for relevance and clarity on a 4-point scale as depicted above.

respectively; or (2) all portions of a composite, conjoined or chimeric flap.

Total free flap failure describes complete loss wherein the donor free flap tissue is unable to survive in the recipient site. Timing of free flap failure in the postoperative period may be characterized as early (within 0–24 h), delayed (within 24–72 h), or late (after 72 h).¹² Arterial failure is most common within the first 24 h and most often related to intraoperative thrombosis, diseased vessels, and mechanical causes. Venous failure is most common within 72 h with mechanical obstruction including compression, twisting, kinking, or vessel stretching as the most common causes of venous occlusion.^{12–14} Late flap failure is an uncommon and unpredictable occurrence, with little to no chance of flap salvage; reported etiologies include pressure-related causes, infection and abscess, and tumor recurrence.^{12,15,16}

1. (B) Partial free flap failure—loss of (1) a component of muscle, skin, or bone in a muscle-only, cutaneous, or osseous flap, respectively; or (2) a portion or whole component of a compound flap including parts of a composite, conjoined or chimeric flap.

Partial free flap failure results from flap compromise in only a portion of the free flap. Partial flap loss occurs from intrinsic factors related to errors in flap design, or extrinsic factors related to mechanics such as compression, twisting, kinking, or vessel stretching, excessive tension during inset, compression of the pedicle, hematoma, or infection.^{17–20} The vascular anatomy of donor tissue sites and their perforator systems may impact these intrinsic and extrinsic etiologies.¹⁷ In partial flap loss, the majority of the flap remains viable indicating adequate perfusion via the main vascular pedicle. Flap edge necrosis measuring ≤ 5 mm does not constitute partial flap failure and is more accurately classified as wound dehiscence.

2. Free flap take back—a subsequent operative procedure to address pending free flap compromise due to a vascular problem intrinsic to the flap or an extrinsic threat to the vasculature of the flap.

TABLE 2 Relevancy and clarity I-CVI scores and modified kappa statistics of proposed nomenclature terms

Item	Term	Relevancy				Clarity				Decision
		I-CVI ^a	Interpretation	P _c ^b	K ^c	I-CVI ^a	Interpretation	P _c ^b	K ^c	
1	Total free flap failure	0.91	Appropriate	0.005	0.91	Excellent	0.002	0.73	Good	Remained
2	Partial free flap failure	0.91	Appropriate	0.005	0.91	Excellent	0.002	0.73	Good	Remained
3	Free flap take back	0.91	Appropriate	0.005	0.91	Excellent	0.003	0.63	Good	Remained
4	Vascular compromise	0.54	Eliminate	0.004	0.54 ^d	Fair	0.009	0.36	Fair	Eliminated
5	Arterial thrombosis	1	Appropriate	0	1	Excellent	0.005	0.91	Excellent	Remained
6	Venous thrombosis	0.91	Appropriate	0.005	0.91	Excellent	0.005	0.91	Excellent	Remained
7	Revision of microvascular anastomosis	0.91	Appropriate	0.005	0.91	Excellent	0.005	0.91	Excellent	Remained
8	Fistula	0.82	Appropriate	0.001	0.82	Excellent	0.002	0.73	Good	Remained
9	Cellulitis	0.64	Eliminate	0.003	0.63 ^d	Good	0.005	0.91	Excellent	Eliminated
10	Surgical site abscess	0.73	Appropriate	0.04	0.73 ^d	Good	0.001	0.82	Excellent	Eliminated
11	Wound dehiscence	0.82	Appropriate	0.002	0.82	Excellent	0.001	0.82	Excellent	Remained
12	Hematoma	0.91	Appropriate	0.005	0.91	Excellent	0.005	0.91	Excellent	Remained
13	Seroma	0.82	Appropriate	0.001	0.82	Excellent	0.001	0.91	Excellent	Remained
14	Partial skin graft failure	1	Appropriate	0	1	Excellent	0	1	Excellent	Remained
15	Total skin graft failure	0.91	Appropriate	0.005	0.91	Excellent	0.005	0.91	Excellent	Remained
16	Exposed hardware or bone	0.91	Appropriate	0.005	0.91	Excellent	0.005	0.91	Excellent	Remained
17	Hardware failure	1	Appropriate	0	1	Excellent	0.005	0.91	Excellent	Remained
18	Malocclusion	0.73	Needs revision	0	0.73 ^d	Good	0.003	0.63	Good	Eliminated
19	Non- or mal-union	0.73	Needs revision	0.002	0.73 ^d	Good	0.005	0.91	Excellent	Eliminated

^aI-CVI: item-level content validity index;

^bP_c: probably of chance occurrence, computed using the formula $P_c = [NI/AI(N - A)] \times 0.5^N$ where N = number of panel experts and A = number of panelists who agree that the item is relevant or clear;

^cK: modified kappa, computed using the formula $K = (I-CVI - P_c)/(1 - P_c)$. Interpretation of I-CVI: >0.79 = Appropriate, 0.70-0.79 = Needs revision, <0.70 = Eliminated. Interpretation criteria for

K > 0.74 = Excellent, 0.60-0.74 = Good, 0.40-0.59 = Fair.

^dItems that achieved adjusted relevancy I-CVI scores (modified kappa, K) <0.74 were eliminated from inclusion in the final set of terms.

Free flap take back describes an unplanned operative procedure (i.e., not scheduled at the time of the index procedure) to address vascular compromise due to an intrinsic factor (e.g., arterial or venous thrombosis in the vicinity of the microvascular anastomosis) or an extrinsic threat (e.g., infection, hematoma). Circulatory compromise, whether intrinsic or extrinsic, risks the viability of the free flap and must be surgically addressed in an attempt to salvage the flap. Arterial and venous compromises are the most common causes of early and delayed postoperative free flap failures, respectively.^{12–14} A return to the operating room to address a nonvascular etiology, such as infection or bleeding, that does not threaten the microvascular anastomosis should not be designated as a flap take back.

3. Arterial thrombosis—a clot in the vicinity of a microvascular anastomosis which compromises blood inflow to a flap.

The formation of clot(s) at or distal to the arterial sites of microvascular anastomosis leads to a disruption in arterial perfusion and vascular compromise of the free flap. Arterial thrombosis is a multifactorial process involving inappropriate intraluminal platelet aggregation at the sites of high shear and turbulent flow, ruptured plaque, or intimal damage.^{12,21} Arterial thrombosis is a surgical emergency and is the most common cause of arterial failure, occurring most often in the early postoperative period within 24 h.^{12–14} The possibility of successful revision decreases as further time elapses from the event.^{12,21} Clinical signs of arterial thrombosis include flap pallor, cool temperature, absence of bright red bleeding with pin prick testing or rubbing a raw wound edge, inability to detect capillary refill, and lack of a pulse detected with doppler monitoring.

4. Venous thrombosis—a clot in the vicinity of a microvascular anastomosis which compromises blood outflow from a flap.

The formation of clot(s) at or distal to the venous sites of microvascular anastomosis leads to a disruption in venous outflow and vascular compromise of the free flap. Venous thrombosis is a multifactorial process involving venous stasis, endothelial injury, and hypercoagulability.^{22–24} The incidence of venous thrombosis is far more common than arterial thrombosis and is often subtle and progresses slowly. Typically occurring within 72 h postoperatively, it is most commonly caused by mechanical obstruction (e.g., external compression or kinking, or head and neck positional changes).^{12–14,24} Return to the operative room for surgical exploration and revision is necessary to salvage a flap from venous failure.²⁵ Thrombotic occlusion of a vein manifests as congested appearance of the flap with cyanotic color changes, increased firmness and edema of the tissue,

excessive bleeding from wound edges, pin prick test revealing brisk, dark blood return, and absent doppler signals.

5. Revision of microvascular anastomosis—a surgical intervention performed on the initial arterial and/or venous anastomosis.

Revision of microvascular anastomosis is a secondary surgical intervention performed on the initial arterial and/or venous anastomosis to re-establish adequate arterial perfusion or venous outflow. Depending on the underlying cause, revision of the microvascular anastomosis includes excising or removing sutures, repeating the anastomosis, flushing vessels with heparinized saline, thrombectomy/thrombolysis, preparation of different recipient vessels, and/or utilizing a Fogarty vascular balloon catheter for vessel dilation.²⁶

6. Fistula—an abnormal communication between two or more spaces, including the term salivary leak.

A fistula represents a pathologic pathway between two or more anatomic sites, such as the oral cavity and skin (orocutaneous), oral cavity and the neck (orocervical) or the pharynx and the cutaneous surface of the neck (pharyngocutaneous).²⁷ In the context of head and neck reconstruction, the term salivary leak is used synonymously with fistula, wherein dehiscence within the upper aerodigestive tract permits escape of salivary fluid into the neck cavity (contained leak), or outside the neck (non-contained leak). Though the terms fistula and salivary leak are used synonymously, it is important to distinguish that not all fistulas are salivary leaks. For example, a tracheoinnominate fistula, described as an aberrant connection between the innominate artery (brachiocephalic trunk or brachiocephalic artery) and the trachea, is a rare and potentially fatal complication described in open and percutaneous tracheostomy procedures, as well as following treatment of advanced hypopharyngeal or cervical esophageal cancers.^{28,29}

7. Wound dehiscence—separation and/or breakdown of a surgical site incision.

Wound dehiscence describes separation of the approximated margins of a surgical incision.³⁰ There is an association between wound dehiscence and smoking, prior radiotherapy (particularly in excess of narrow-field techniques), and poor preoperative nutritional status.^{31–33} In the context of head and neck reconstruction, neck incisional dehiscence may present secondary to fistula formation, salivary leak, and/or infection. It is important to distinguish that wound dehiscence is not synonymous with fistula. Although a wound dehiscence can manifest as part of a local surgical site infection (SSI), the terms are not one and the same. Superficial incisional SSI^{34–37} is limited to the skin or subcutaneous tissue of the surgical incision. Deep incisional SSI^{34–37} involves the deeper soft tissues such as fascial and muscle layers. Infection

involving any part of the anatomy, other than the incision, which is opened and manipulated during an operation, is classified as an organ space SSI.^{34–37} Pain or tenderness, localized swelling, erythema, cellulitis, purulent drainage, and abscess formation are absent in the context of a wound dehiscence that is not part of an SSI.

8. Hematoma—collection of blood in tissues in a surgical site.

Hematoma is a localized collection of blood, usually clotted, in an organ, space, or tissue.³⁰ Many hematomas occur within the first 24 h and are commonly detected within the first five postoperative days.^{38–40} Delayed hematomas may result from delayed or missed detection, coagulopathy, or the need for anticoagulation postoperatively due to medical or free flap reasons.⁴¹ Early recognition of hematomas is crucial as they can precede wound infection, wound dehiscence, and fistula formation, and ultimately can lead to flap compromise and tissue necrosis if unattended.⁴² Early detection of hematomas and operative intervention corresponds to higher flap salvage rates.^{38,41,43,44}

9. Seroma—collection of serous fluid in tissues in a surgical site.

Seroma is a collection of serum, defined as the fluid and protein-rich component of blood that is not involved in clotting.³⁰ The potential space produced from tissue and lymphatic channel disruption promotes the collection of exudative fluid.⁴⁵ Large seromas can cause local distention and significant pain, but may go unrecognized given the expected localized swelling, tenderness, and discomfort following head and neck reconstructive surgery. Left unaddressed, seromas can lead to wound infection and dehiscence as well as flap necrosis. Careful wound closure with obliteration of dead space may reduce the likelihood of seroma formation.⁴⁵

10. (A) Total skin graft failure—unsuccessful integration of the entirety of a split- or full-thickness graft into the wound bed, resulting in complete necrosis and loss of the graft.

Elements involved in successful graft take include a sufficiently vascularized wound bed, placement of the dermal graft side down in contact with the recipient bed, prevention of hematomas or seromas, minimization of shearing forces and motion at the recipient site, and infection prevention.⁴⁶ Technical errors such as stretching the graft too tightly causing tenting, and improper placement of bolster material, can prevent optimal apposition with the wound bed. Hematoma or seroma formation is a common contributor to graft failure as these collections reduce graft adherence to the wound bed and neovascularization. Smoking and diabetes mellitus type 2 have been associated with decreased graft survival.⁴⁷ The most common etiologies of total graft failure include placement on radiated tissue,

exposure to cortical bone without periosteum, cartilage without perichondrium, tendons without peritenon, and infection of the wound bed.⁴⁶

10. (B) Partial skin graft failure—unsuccessful integration of a portion of a split- or full-thickness graft into the wound bed, resulting in partial necrosis and loss of the graft.

Graft failure can be measured as a percentage of skin area that is lost postoperatively, or it can be measured in a more binary manner where failure of the initial graft necessitates repeated skin grafting. Skin grafts with less than 100% integration are classified as partial graft failure. Factors related to partial skin graft failure are the same for total failure (refer to 10.A).

11. Exposed hardware or bone—dehiscence of soft tissue surrounding implanted hardware or native and/or implanted bone, respectively.

Hardware exposure is commonly accompanied by wound dehiscence along free flap suture lines at the reconstructed site; though, there are also reports of hardware eroding through native tissue postoperatively.⁴⁸ Patients who experience hardware or bone exposure are often at an increased risk of poor wound healing due to a history of radiation therapy or smoking.^{49–51} Exposed bone is most common in the setting of osteoradionecrosis (ORN). Devitalization and necrosis of bone and/or surrounding soft tissue results in areas of chronically exposed bone and nonhealing infections which may require hardware explantation to eliminate the nidus of infection.^{52–54}

(12) Hardware failure—screw and/or plate loosening, deformity, migration, and/or fracture.

While extrusion or exposure of hardware is considered a wound healing complication, events such as hardware loosening, fracture, and migration can be categorized as fixation failures.^{55,56} Implanted hardware is used to span continuity defects or stabilize donor-recipient osteotomy sites in maxillomandibular reconstruction. Over-manipulation of fixation devices to fit patient-specific contours, individual implant defects, and unequally applied forces by the muscles of mastication can contribute to hardware failure. Hardware failures may manifest as loose screws, migration of fixation devices through adjacent tissues, or plate fractures.^{53,57} Plate fracture is unusual outside the setting of previous radiotherapy treatment and ORN.⁵⁸ Management of hardware failure varies with the severity of the complication.

4 | DISCUSSION

In order to maximize utilization of outcomes data to improve the quality of care delivery, the outcomes must

be adequately defined. This task has proven challenging in the field of head and neck reconstructive surgery given the lack of consensus among surgeon colleagues. In fact, the discordance and discussions surrounding definitions—and even, which terms to include—among our panel members exemplifies the need for a nomenclature paradigm. Clinical consensus surveys were conducted through an iterative process among a panel of head and neck and facial plastics and reconstructive surgeons to create a nomenclature paradigm to describe free flap complications in microvascular head and neck reconstruction.

Panel member discussions regarding the term “fistula” (I-CVI = 0.73), highlight the uniqueness of complications in the setting of head and neck reconstructive surgery. Primary tumor stage, neoadjuvant radiotherapy exposure, duration of surgery, surgical site infection, malnutrition, hypothyroidism, and diabetes are known risk factors for fistula formation.^{59–61} Panelists agreed that a fistula in the head and neck patient following reconstructive surgery represents a salivary leak. Less clear cut, however, was the necessity for this abnormal connection to be epithelial-lined, which has been described in the thoracic literature to classify fistulas.⁶² The specificity of the term “fistula” as a salivary leak in the head and neck was further reiterated in clarification of the term “wound dehiscence” (I-CVI = 0.73). Here, panelists noted that dehiscence of a surgical wound or incision site does not encompass a “fistula.” In other words, cutaneous breakdown secondary to a noncontained salivary leak should not be described as a “wound dehiscence.” Similarly, in the absence of signs or symptoms of infection, a “wound dehiscence” does not always represent a local SSI.

We emphasize that this nomenclature paradigm is not intended to be a diagnostic or treatment guideline. By developing and clarifying a set of commonly used terms to describe free flap complications, this initiative serves as (1) a catalyst for providers to adopt these working definitions in practice, and (2) a call to action to incorporate these terms as outcomes measures into commonly used national databases. For example, ACS-NSQIP created the Procedure Targeted program specifically to allow incorporation of procedure specific variables and outcomes. It presents a unique opportunity to utilize consensus nomenclature in an established database in order to improve our ability to report, assess and compare outcomes specific to head and neck reconstructive surgery. A Procedure Targeted group for head and neck oncologic surgery within the ACS-NSQIP database does not currently exist but is made possible by collaborative endeavors such as this. It represents an important next step toward improving the quality of care delivery for

patients undergoing head and neck reconstructive surgery and it is the intention of the authors to consider developing such a group moving forward.

Less obvious, but also critical, to this endeavor is the educational benefit that is derived from consistent names and definitions of common free flap complications. This nomenclature paradigm serves as an invaluable teaching tool for trainees and caregivers (e.g., nurses, advanced practice providers) as they understand and perform free flap assessments and develop the ability to manage associated complications. Frame semantics is a theoretical model for how we understand the meaning of words.⁶³ In this model, Fillmore identifies words as “frames” which trigger mental images, known as “scenes,” that are associated with past experiences and knowledge. The mental maps we form of words and associated concepts – of frames and scenes – allows us to draw appropriate conclusions about what those words mean and increase the clarity in our communication surrounding those words. A fundamental assumption underlying frame semantics is that in order to understand the meanings of words in a language, we must first have the knowledge of the concepts and background underlying those words. The terms and supporting descriptions presented herein serve as a cognitive structuring tool, providing the background knowledge for these complications, how these terms should be used, and the implications of these words on the care of our patients.

5 | CONCLUSION

Standardized reporting in the field of head and neck reconstructive surgery not only allows for more effective documentation in the electronic medical record, but also encourages multi-institutional research collaboration, larger scale quality improvement initiatives, the ability to set risk-adjusted benchmarks, and enhances education and communication between providers, patients, trainees, and colleagues. Use of a nomenclature paradigm allows us to speak the same language and decrease the “language barriers” that can hinder potential improvements in the care and outcomes of our patients.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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