

HEAD AND NECK

Management of nasal vestibule carcinomas: recommendations by the Oncological Committee of the Italian Society of Otorhinolaryngology – Head and Neck Surgery

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SUMMARY

Objective. Squamous cell carcinoma of the nasal vestibule (NV SCC) is a head and neck malignancy for which there is no established consensus on most aspects of clinical management. The purpose of this document is to give updated recommendations that incorporate recent evidence on its clinical characteristics and the high efficacy of brachytherapy as primary treatment modality.

Methods. A working group consisting of the members of the Scientific Committee for Oncology and Reconstructive Surgery of the Italian Society of Otorhinolaryngology Head and Neck Surgery and radiation oncologists expert in brachytherapy was formed to achieve a consensus.

Results. Consensus was reached on a set of recommendations, proposing a refined anatomical definition of the nasal vestibule, a novel T staging system of the NV SCC, and brachytherapy as standard of care, with a new method for catheter implantation.

Conclusions. The Committee emphasises the critical role of an accurate classification in clinical practice and encourages further research to validate the novel staging system and further improve treatment strategies. Where appropriate, it is recommended that patients be referred to centres with specific experience in brachytherapy for NV SCC.

KEY WORDS: nasal cancer, nasal vestibule cancer, brachytherapy, radiation therapy, squamous cell carcinoma

Introduction

Squamous cell carcinoma (SCC) of the nasal vestibule (NV) is considered a relatively rare malignancy, accounting for approximately 1% of all head and neck cancers ¹.

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The NV, which is the most anterior part of the nasal cavity, consists of three walls (medial, lateral, and inferior) and has a framework made by nasal cartilages. Through these structures, NV SCC can directly spread to the skin², which results in frequent misdiagnoses with skin primaries. Notably, the initial onset of a small, inapparent primary lesion in the NV can easily be a more evident outer skin invasion of the nasal pyramid (Fig. 1). Furthermore, despite being part of the nasal cavity, the NV's inner lining consists of epidermis up to the level of the limen nasi, which may contribute to the confusion with skin primaries. There is no consensus on the treatment of choice of this tumour, and only a few series specifically focus on this disease⁴⁻⁷.

However, in recent years, there has been a growing interest towards the specific features of SCC involving the NV, and the challenges surrounding its management – from diagnosis to classification, staging and treatment^{3,8-10}. This increased focus, primarily driven by Italian and Dutch researchers^{8,9,11,12}, provided data leading the Scientific Committee for Oncology and Reconstructive Surgery of the Italian Society of Otorhinolaryngology Head and Neck Surgery to produce the present document with a series of recommendations, which in the authors' view can establish a state-of-the-art management of NV SCC.

Materials and methods

A position statement working group (FB, GM, MFC, CL, LP, PN) was created by the Scientific Committee for Oncology and Reconstructive Surgery of the Italian Society of Otorhinolaryngology Head and Neck Surgery, which included Otolaryngologists with specific interest in the management of NV SCC. Two radiation oncologists (LT, AG) were also included in the group.

After excluding potential conflicts of interest, the working group was tasked with the objectives of position statements. A literature search was initiated using PubMed, Cochrane, and Google Scholar search engines. Search terms incorporated: nasal vestibule cancer, nasal cancer, surgical approaches, radiation therapy, brachytherapy, chemotherapy, and immunotherapy. The inquiry included clinical trials, cohort studies, and review articles. The review was extended to current national and society guidelines and published position statements from the gray literature.

Throughout the span of two online meetings and additional electronic group correspondence, the literature search results were compiled into shared themes and formal position statements for the Italian Society of Otorhinolaryngology Head and Neck Surgery were drafted. Areas of ambiguity, controversy, and inconsistency within the literature were highlighted for discussion within the working group.



Figure 1. Predominant skin manifestations of primary nasal vestibule cancer (from Bussu et al., 2023, mod.)³.

After the review, discussion, and revisions, the working group reached a unanimous consensus on the position statements. The document was submitted to the Scientific Committee for Oncology and Reconstructive Surgery and formally approved.

Results

Statement 1. A clear anatomic definition

Data reported in the literature on the incidence of NV SCC are misleading. This is in large part due to the lack of a universally accepted definition of NV anatomical boundaries. This ambiguity contributes to an unclear definition of the disease. To address this issue, **the Committee agrees to adopt a plane tangential to the piriform opening as the posterior boundary, a landmark that is easily identifiable through imaging studies**^{3,9,13}. This boundary demarcates the NV from the proper nasal cavity (Fig. 2). Additionally, the limen nasi and the edge of the nostril should be recognized as the boundaries separating the NV from the skin of the nose and upper lip, respectively.

Statement 2. Nasal vestibule cancer as a distinct entity

The current International Classification of Diseases for Oncology (ICD-O) fails to adequately distinguish NV cancer from other nasal and paranasal cancers, as the NV is currently considered an unspecified area within the nasal cavity¹⁴.

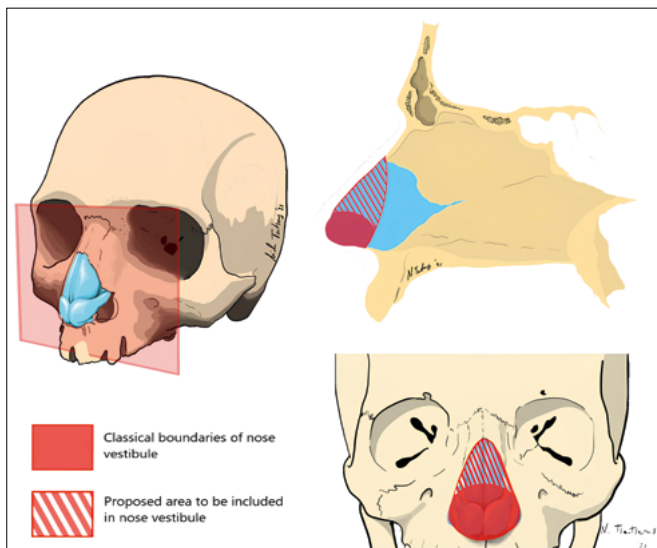


Figure 2. Defining distinct anatomical boundaries for the nasal vestibule (NV). This figure proposes clear boundaries for the NV also to improve estimation of the incidence of NV carcinoma (from Parrilla et al., 2023, mod.)¹⁴.

Specifically, the ICD code C30.0 groups NV with the nasal cavity, making it difficult to accurately assess and track the prevalence and incidence of NV cancer among other nose cancers¹⁵. Consequently, the absence of a specific World Health Organization (WHO) topographic code allegedly leads to underestimate NV cancer prevalence. **The present Committee strongly advocates for the introduction of a specific topographic code for NV within the WHO ICD-O.**

Statement 3. Avoiding misdiagnosis

The frequent misdiagnosis of NV carcinomas as skin primaries not only contributes to underestimate the incidence of the disease but can also lead to improper treatment of NV SCC as skin cancer, potentially resulting in both cosmetic and oncological disasters (Fig. 3). In fact, there are key differences in tumour spread between NV and skin cancer. NV cancer preferentially spreads along the cartilages, which cannot be spared, whereas skin primaries tend to remain superficial to the cartilages due to their anatomic structure and most often allow their sparing^{2,4}. Notably, skin involvement by NV cancer can be very early even in case of small inapparent lesions inside the nose¹³. As such, **the Committee strongly recommends that all skin lesions in and around the nose tip and nostrils, especially those diagnosed as SCC, should be evaluated by an otolaryngologist to exclude a primary nasal lesion**^{3,9}.

Statement 4. A specific nasal vestibule cancer classification

Currently, there is no universally accepted staging system for NV SCC, particularly concerning T classification. The most utilized staging systems include the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system for nose and paranasal cancers, the UICC/AJCC staging system for non-melanoma skin cancer (NMSC) of the head and neck, and the Wang's classification^{15,16}. Among these, the Wang's classification, that was developed specifically for the NV approximately 50 years ago, has proven to be the most re-



Figure 3. Cosmetic and oncologic consequences of misdiagnosed nasal vestibule cancers treated as primary skin cancer (from Bussu et al., 2023, mod.)³.

liable in predicting survival outcomes for NV SCC^{7,13,17}. This is because of the unique features of NV malignancies (distinct patterns of spread and prognostic factors), which result in early skin involvement and late bone involvement. This behaviour differentiates NV from other malignancies within the same anatomic region, such as those of the nasal cavity proper and the ethmoid, classified with the same criteria by UICC/AJCC, where skin involvement is rare, late and with a much more ominous impact on prognosis. Figure 4 illustrates some of the unique NV patterns of spread to the skin¹⁸. Current UICC/AJCC staging systems fail to adequately capture these nuances, which emphasises the necessity for tailored parameters. Applying the same parameters used for nasal cavity proper malignancies does not reflect the characteristics of NV malignancies and leads to inaccuracies in diagnosis and treatment planning. However, despite its comparative superiority to the UICC/AJCC staging system, the Wang's classification, which is admittedly dated, has its own limitations. It lacks clear anatomical boundaries for the site, and its three-tiered structure makes integration with the UICC/AJCC TNM difficult¹⁶. Additionally, it employs an ambiguous terminology (e.g., "massive" or "large portion"), which hampers standardisation and quantification and can make the discrimination between T2 and T3 subjective¹⁶. Therefore, there is an urgent need to revise the classification and staging of NV cancer and develop a new system that better accounts for the unique anatomical and clinical characteristics of such a malignancy. Recently, an Italian group has proposed a new T classification system that aligns with these principles (Tab. I)^{9,10}. This proposal includes clear anatomical landmarks that can be easily identified on radiological images and specific prognostic factors that were already present in Wang's classification, and in particular the early skin involvement and the late, ominous bone involvement, both characteristic of this malignancy. The new classification is four-tiered for T with the perspective of an integration in the global UICC/AJCC staging system⁹. Such an approach would

not only improve the accuracy of disease staging but also contribute to a better understanding of its progression and prognosis, thereby informing more effective and personalized treatment strategies for patients with NV carcinomas. The Committee strongly recommends **the routine use of the validated Wang's classification and encourages the concomitant adoption of this novel classification**. This will build evidence for validation of the latter, facilitate its potential future widespread adoption, and eventually support its incorporation into the comprehensive UICC/AJCC staging system.

Statement 5. Brachytherapy as standard of care

Treatment outcomes should be assessed in a hierarchical manner, prioritising oncological results, followed by functional and cosmetic results. Cosmetic outcomes are particularly significant in the context of the NV. Given that the nose is centrally located on the face, where both light and human gaze often focus, even minimal changes are readily noticeable. Significant nasal deformities can greatly affect first impressions and social interactions^{19,20}. Research has demonstrated the influence of nasal appearance on self-identity and mental health, underlining the critical need to ensure acceptable cosmetic outcomes^{19,20-22}.

Radiation and surgery currently represent the two primary treatment options for NV carcinomas^{8,9,11,13,23-25}. Comparative studies report disease-specific survival (DSS) rates between 52% and 94% across three modalities: surgery, external beam radiotherapy (EBRT), and brachytherapy (BT) which in its modern form is now defined as interventional radiotherapy (IRT)^{9,11,13}. Treatment choice typically depends on the resources and expertise available at the treating facility.

When surgery is selected, in view of the specific pattern of spread of NV SCC among cartilages with early skin invasion (Fig. 4) a thorough resection of the ala/nasal wall is most often indicated. This will require complex reconstructive surgeries or the creation and fitting of a bone-anchored

Table I. Bussu et al.'s Nasal Vestibule Tumour (T) Staging System.

T1	The lesion is limited to the nasal vestibule internal surface (skin and or mucosa)
T2a	The lesion invades superficial structures outside the nasal cavity (skin and/or subcutaneous tissue) and in particular upper lip, philtrum, skin of the nose and/or nasolabial fold, but does not destroy cartilage, nor invades bony structures, nor structures beyond the plane of the piriform aperture (septum, lateral wall, turbinates, etc.)
T2b	Disruption of cartilages is evident, without invasion of bony structures, nor of structures beyond the plane of the piriform aperture (septum, lateral wall, turbinates, etc.)
T3	The lesion extends posteriorly beyond the piriform aperture (septum, lateral wall, turbinates, etc.)
T4a	The lesion invades bony structures as hard palate, nasal bones, frontal process of the maxilla, ethmoid, orbit
T4b	Tumour invades any of the following: orbital apex, dura, brain, anterior and middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

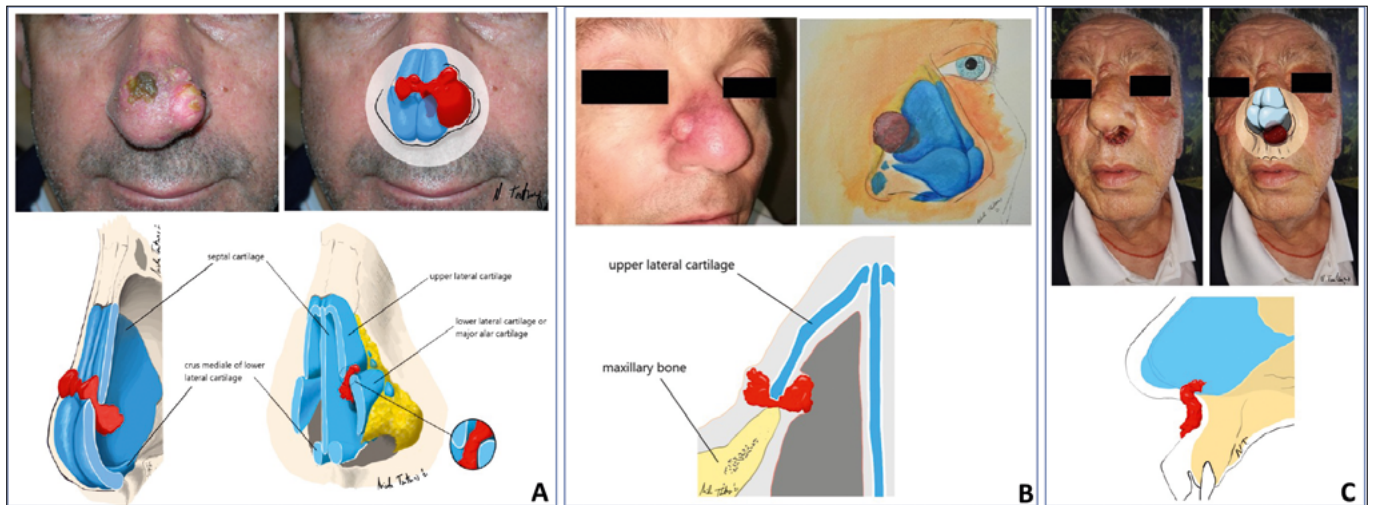


Figure 4. Typical patterns of spread to the skin of nasal vestibule carcinomas. (A) Pathway from the lateral wall of the nasal vestibule to the skin, with the tumour invasion front sliding between the alar and lateral nasal cartilage; (B) Pathway from lateral wall of the nasal vestibule to the skin, with the tumour spreading between the lateral nasal cartilage and the nasal bone; (C) Direct pathway from the nasal septum/columella (medial wall)/floor of the nasal cavity (inferior wall of the nasal vestibule) to the skin of the upper lip (from Bussu et al., 2023, mod.)¹⁸.

epithesis²⁶⁻²⁸. Replicating the nose tip's shape and structure through reconstructive surgery after its complete removal is exceptionally challenging, requiring the restoration of three layers: the inner mucosa, the overlying skin (notably thin and virtually lacking subdermis), and the somewhat hard cartilaginous framework, each with varying degrees of flexibility and a complex three-dimensional shape, accentuated by reliefs and hollows.

In numerous case series and comparative studies, BT has demonstrated non-inferiority to upfront surgery in terms of local-recurrence-free survival (LRFS) and DSS, while providing superior local control compared to EBRT^{6,8,11,12,17,23-25,29-33} (Evidence level: IIA). This evidence is particularly compelling in cases without bone involvement^{17,33}.

Functional parameter analyses among EBRT, BT, and control subjects show no significant differences in nasal flows and resistance²⁴. BT patients are spared the nasal crusting often seen in EBRT patients, and they maintain unchanged Threshold Discrimination Identification (TDI) scores, reliable indicators of the olfactory function, and normal mucociliary clearance, unlike EBRT patients²⁴ (Evidence level: IIB).

On the other hand, cosmetic outcomes strongly favour IRT over surgery^{12,34}. Consistently, cosmetic satisfaction among IRT patients has been reported as significantly superior to that of surgical patients¹⁷ (Evidence level: IIB).

Also, the NV's anatomical characteristics make it well-suited for IRT. The absence of adjacent vital structures allows for the delivery of high radiation doses without causing significant collateral damage. The cartilaginous framework's natural resistance to radiation further supports IRT use and

explains the excellent cosmetic results (Fig. 5) of the procedure due to the preservation of the nose tip's cartilaginous structure.

The clinical target volume's accessibility and the simplicity of tube placement, even under local anaesthesia, render IRT a feasible option for elderly or frail patients as well.

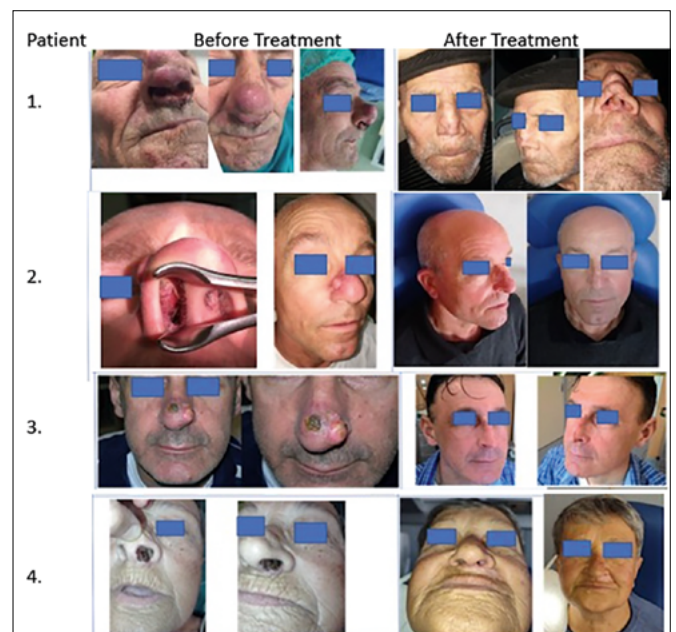


Figure 5. Examples of local control, framework preservation and consequent cosmetic outcomes after IRT for nasal vestibule carcinomas (from Bussu et al, 2023, mod.)³.

This is particularly relevant considering global demographic shifts, including the aging baby-boomer population in the Western Countries^{35,36}.

Based on these findings, the Committee strongly recommends considering IRT as a treatment option for primary NV lesions without bone involvement, as it appears equivalent to surgery for oncological outcomes but offers clear advantages in terms of anatomic preservation and cosmetic results³.

Statement 6. Management of nodal metastases

As in all head and neck malignancies, nodal involvement in NV carcinoma is one of the main prognostic determinants and one of the main reasons for oncological failure.

The lymphatic drainage of the anterior third of the nasal cavity primarily feeds into the facial, submandibular, and, to a much lesser extent, parotid lymph nodes. At diagnosis, about 5-10% of patients with NV carcinoma show lymph node metastases^{7,37-39}, although the detection method is not always specified in these studies.

There is currently no agreed-upon elective treatment for N0 neck in NV SCC. Both surgical clearance and elective nodal irradiation (ENI) are considered potential options. However, current evidence shows that even if nodal metastases are clearly associated to impaired survival, most delayed nodal relapses can anyway be effectively salvaged^{40,41}. **The Committee strongly recommends a careful work up of the neck based on morphological imaging (ultrasound, contrast enhanced magnetic resonance [CE MR] and/or computed tomography [CT]). In case of doubts, the Committee outlines the value of positron emission tomography (PET) CT and of ultrasound guided fine needle aspiration biopsy (FNAB)⁴². Properly staged cN0 neck can be observed, while the Committee strongly recommends neck dissection in cN+ cases, with possible adjuvant treatment based upon the final histological report.** Neck dissection can be performed at the same time of the implantation of IRT plastic tubes.

Statement 7. The anatomic implantation in nasal vestibule IRT

As we discuss the benefits and potential challenges of IRT in NV SCC treatment, it is essential to provide a clear and concise overview of the technique for otolaryngologists who will work closely with radiation oncologists to deliver treatment.

Brachytherapy is a form of radiation therapy that involves placing radioactive sources directly into or near a tumor. This method allows for the delivery of high doses of radiation to the tumour while minimising exposure to the surrounding healthy tissues. The technique can be either interstitial (implanted within the tumour) or endocavitary (implanted within a body cavity close to the tumour).

In the last decades brachytherapy evolved from the direct implantation of radioactive sources, with obvious dosimetric and radioprotection issues and poor control on the effective dose released, to the so called *remote – afterloading machines*, based on the implant of applicators or catheters (plastic tubes in case of NV) in which the source is subsequently inserted to deliver the dose without exposure to ionising radiation by healthcare staff. By controlling the dwell time in each position in the catheter using dedicated software, it is possible to optimise the dose distribution achieving an intensity-modulated technique.

To obtain the best dose distribution the implants for interstitial IRT have traditionally been placed following dosimetry systems, the main ones being Manchester and Paris systems. Paris system is the most popular in case of flexible implants and is based on the following main principles: 1) the active sources (plastic tubes in modern IRT) should be parallel and straight; 2) the sources should be inserted equidistant each others. Applying the Paris system to the nose implies piercing nasal walls and septum in many points. However, it is well known to otolaryngologists that piercing the mucoperichondrium leads to the destruction of the cartilage, the risk of which is even higher because the points of passage are the ones with the highest dose delivered (closest to the tubes). In fact, in the BT series with implants done according to the Paris system a high rate of septal and even alar perforation is reported¹³.

An Italian group developed a new concept of anatomical implantation for nasal primaries based on the following principles:

1. The tubes must be interstitial as much as possible;
 2. Do not pierce the perichondrium, ideally remaining along the subperichondral planes of (rhino-)septoplasty.
- These two rules have been shown to avoid perforations^{9,13,25} and are also associated to the best stability of implants, which is a fundamental requirement for the reliability of the treatment plan (Evidence level: III)^{9,13,24,43,44}.

If “fully interstitial/buried” implants are not sufficient for adequate clinical target volume (CTV) coverage by overreaching all the limits of the lesion, other tricks can be used to stabilize the tubes. One of these situations is determined by the presence of a bulky skin spread; in this case the issue can be solved with a “contact” strategy, by placing the tubes on the skin in the area of such superficial spread and stabilising them with an interstitial course on both sides. The most common of these situations is given by the extension of the lesion posterior to the limit of the nasal vestibule, which is the plane tangential to the piriform opening. In these cases, a fully interstitial implant placement may not be possible because of the bony structures, thus endocavitary implantation may be needed. This approach, however, raises concerns about the

stabilization of the tubes and high doses to the mucosal surfaces can be associated in our experience with synechia. To address the issue of stabilisation of endocavitary implants, blind catheters can be fixed to Meroceal packing, though this may result in unpredictable geometry and path of the tube and consequent undesired issues with CTV coverage. Alternatively, blind tubes can be secured to a silicone foil, maintaining a precise relationship between the catheters. Endocavitary molds, first suggested by Haynes in 1974⁴⁵, may also provide a solution for increasing stability and reliability and expanding the indications for IRT in more posterior nasal cavity primaries.

The Committee strongly recommends following the above rules for anatomic implantation when treating NV SCC by interventional radiotherapy.

Conclusions

In the absence of high-quality, level I Evidence for NV SCC and in consideration of the critical issues and clear lack of a unifying rational approach to these tumors at an international level, the Committee produced this position paper to assist physicians in the management of this under-recognised, ambiguously defined, yet potentially devastating oncological disease.

A proper classification in daily clinical practice is essential to bolster evidence. Building on this, the Committee urges clinicians to diligently pursue the outlined priority research areas to enhance NV SCC management^{11,12,17}. We also encourage participation in ongoing clinical trials or the inception of novel ones to further build evidence.

If the best treatment options are not readily available in certain Italian facilities, the Committee strongly recommends referring patients to centers possessing the necessary technology and expertise to provide optimal treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

FB, LT, GM: conceptualization; FB, LT, GM: methodology; FB, LP, GM: validation; FB, MFC: resources; FB, MFC, CL, G: writing – original draft preparation; FB, MFC, CL, GM: writing – review and editing; FB, LT, RP, PG, GM, AG, FC, GA, FL, LC LP, PN, GB: supervision. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

This research was conducted in full accordance with the World Medical Association Declaration of Helsinki (2002). Due to the nature of this study, the Institutional Review Board of the participating Hospitals do not perform a formal ethical assessment.

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