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A novel technique for conducting flexible bronchoscopy cryobiopsy under conscious sedation

An observational study

Francesco Salton, MD[a,*], Marco Biolo, MD[a], Liliana Trotta, MD[a], Lucrezia Mondini, MD[a], Alessia Giovanna Andrisano, MD[a], Nicolò Reccardini, MD[a], Paola Confalonieri, MD[a], Caterina Antonaglia, MD[a], Marco Confalonieri, MD[a], Barbara Ruaro, MD, PhD[a]

Abstract

Transbronchial lung cryobiopsy (TBCB) is a reliable method for obtaining histopathological findings in interstitial lung diseases. TBCB is traditionally performed during rigid bronchoscopy, positioning an endobronchial balloon blocker to facilitate bleeding management. Therefore, it can be challenging to implement in Centers without access to anesthesiologic support or dedicated beds for endoscopic procedures. We present a series of 11 patients who underwent 12 TBCBs using a flexible bronchoscope and a 5 Fr endobronchial blocker passing through an uncuffed endotracheal tube, under moderate sedation and spontaneous breathing. All procedures were carried out in an endoscopy suite, using fluoroscopy guidance but without requiring anesthesiologic assistance. TBCB was feasible in all cases, and it demonstrated similar or improved diagnostic yield (90.1%) and safety compared to rigid bronchoscopy. In 1 case, it was successfully repeated due to an inconclusive histological definition at the first attempt. The size of the samples was consistent with the literature, as it was the incidence of pneumothorax (16.6%). Four cases of moderate bleeding and 4 cases of severe bleeding were managed without further complications. To our knowledge, this is the first description of a technique allowing to perform TBCB through an artificial airway without need for either rigid bronchoscopy or general anesthesia. We believe this technique could make TBCB faster, cost-effective, and feasible even in resource-limited settings without compromising on safety. However, further studies are needed to validate these findings.

Abbreviations: CPAP = continuous positive airway pressure, CT = computed tomography, EBB = endobronchial balloon blocker, ECG = electrocardiography, ETT = endotracheal tube, HFNC = high-flow nasal cannula, ILD = interstitial lung disease, SD = standard deviation, SLB = surgical lung biopsy, TBB = transbronchial biopsy, TBCB = transbronchial lung cryobiopsy.

Keywords: conscious sedation, cryobiopsy, endobronchial blocker, flexible bronchoscopy, ILDs

1. Introduction

Transbronchial lung cryobiopsy (TBCB) is now widely acknowledged as a dependable alternative to surgical lung biopsy (SLB) for providing histopathologic findings in multidisciplinary discussions on interstitial lung diseases (ILDs).[1,2] TBCB offers several advantages over SLB, including shorter hospitalization times, higher safety and overall cost-effectiveness.[3] In comparison to other endoscopic techniques like forceps transbronchial biopsy (TBB), TBCB allows for the retrieval of larger specimens with less crush artifacts, resulting in a higher diagnostic yield.[4–6]

The TBCB procedure involves a flexible, insulated catheter with a blunt metal tip that can be advanced through the working channel of a flexible bronchoscope. The metal tip rapidly cools down as compressed cryogen gas is released through the probe, enabling the freezing of surrounding lung tissue within seconds. This frozen tissue is then removed en bloc from the airways.[7] Although

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Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

[a] Department of Medical Surgical and Health Sciences, Pulmonology Unit, University Hospital of Cattinara, University of Trieste, Trieste, Italy.

* Correspondence: Francesco Salton, Pulmonology Unit, Department of Medical Surgical and Health Sciences, University Hospital of Cattinara, University of Trieste, Strada di Fiume, 447, Trieste 34149, Italy (e-mail: francesco.salton@asugi.sanita.fvg.it).

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pneumothorax and bleeding are the most common complications, occurring in 2.6% to 20.2% and 1.8% to 47% of cases, respectively, the overall safety profile of the procedure remains favorable.[8,9]

According to the latest expert panel report, TBCB is best performed through a rigid bronchoscope, with a prophylactic balloon placed in the segment feeding the target area. Inflation of the balloon immediately after retrieving the cryoprobe and flexible bronchoscope from the airways helps reduce the risk of bleeding and enhances procedural safety.[10] Alternatively, TBCB can be conducted through an endotracheal tube (ETT), with an endobronchial balloon blocker (EBB) passed through an extra channel of the ETT.[10] In both cases, general anesthesia is recommended to enhance patient tolerance and prevent excessive coughing, which could otherwise complicate the management of potential hemorrhages.[10,11] Consequently, TBCB is typically performed under invasive mechanical ventilation with anesthesiologic assistance, either in an operating room or an endoscopy suite. This approach necessitates hospital admission and post-procedural recovery in a controlled environment, resulting in relatively high costs.[12] Moreover, general anesthesia may be associated with complications during intubation, induction, mechanical ventilation, as well as difficulties during extubation or exacerbations of preexisting chronic obstructive respiratory diseases. The availability of an anesthesiologist and/or an operating room could be limited in certain hospitals, especially during specific circumstances like the resource constraints faced during the COVID-19 pandemic.[13,14] Altogether, these factors hinder the wider accessibility to TBCB urged by current guidelines for the differential diagnosis of ILDs.[15]

Although some reports exist of TBCB being performed with a flexible bronchoscope under moderate sedation and spontaneous breathing, these cases did not involve the positioning of an ETT and/or an EBB, potentially making the procedure unsafe in the event of severe bleeding because a second access through the glottis is necessary after the biopsy.[16–18] In this study, we propose a new technique to perform TBCB using a flexible bronchoscope and an EBB through an ETT in moderately sedated and spontaneously breathing patients, without the need for anesthesiologic assistance.

2. Methods

This case-series includes 11 consecutive patients who were referred to the interventional pulmonology unit of the University Hospital of Trieste for TBCB to aid in the differential diagnosis of ILDs following a multidisciplinary discussion, from April 2022 to June 2023. We present this study in accordance with the STROBE reporting checklist.

Since the described technique represents the standard of care at the study Center, approval from the referral Ethics Committee was waived. However, all patients provided written informed consent for both the procedure and for data collection, analysis and publication. All relevant data were manually extracted from electronic patient registers and anonymously coded into a standardized data collection form.

The TBCB procedure was performed in an endoscopy suite by 1 expert interventional pulmonologist and 2 nurses, as anesthesiologic assistance was unavailable at the study Center. The initial planning, risk assessment, and selection of the biopsy site based on chest CT findings were conducted individually by the interventional pulmonologist for each patient. All patients underwent routine laboratory tests, electrocardiography (ECG), diffusing capacity for carbon monoxide, and chest CT within 1 month before the TBCB procedure. Pre-procedural management, including fasting and suspension of anticoagulant and antiaggregant therapy, followed the latest guidelines as per the Center usual practice.[11]

Throughout the procedure, continuous monitoring of peripheral oxygen saturation (SpO_2), respiratory rate, heart rate, blood pressure, and ECG was ensured. Supplemental oxygen was administered via high-flow nasal cannula (HFNC) with an inspired fraction of oxygen (FiO_2) ranging from 50% to 80% and a flow rate of 60 liters per minute. Additionally, a mechanical ventilator was readily available in the endoscopy suite. If necessary to maintain SpO_2 levels above 90%, a continuous positive pressure (CPAP) of 6 cm H_2O with FiO_2 ranging from 60% to 100% was applied through the ETT while keeping the cuff deflated.

Moderate sedation was achieved by titrating midazolam and fentanyl to the lowest effective dose, following the guidelines of the British Thoracic Society. Local anesthesia with 2% lidocaine was administered through intranasal nebulization and intratracheal boluses up to a total volume of 30 mL.

The patient was intubated with a 7.5 mm ETT while keeping the cuff deflated to allow for spontaneous breathing. A 5 Fr EBB (Arndt endobronchial blocker set, Cook Medical, Bloomington, IN, USA) was then positioned at the entrance of the selected segmental bronchus and secured at the correct distance using a threaded locking system. The EBB set included a proprietary Y junction that allowed the bronchoscope and the blocker to enter the ETT through separate channels (Fig. 1). A nurse was trained to inflate the balloon with the appropriate amount of air to ensure a watertight blockade of the airway after TBCB.

TBCB was performed using a 4.9 mm outer diameter bronchoscope (Pentax FB-15V, Pentax Medical, HOYA Corporation, Tokyo, Japan) and a 1.7 mm cryoprobe (ERBE, Tübingen, Germany) under fluoroscopy guidance. The tip of the cryoprobe was positioned 2 cm from the pleura, and freezing time was 9 seconds. Subsequently, the bronchoscope and cryoprobe were removed together en bloc from the ETT. Immediately after retraction of the bronchoscope, the nurse inflated the EBB to the predetermined amount of air. The bronchoscope was then reinserted through the ETT, and the balloon was deflated to assess bleeding occurrence. The main steps of the procedure are illustrated in Figure 2. At least 2 TBCB samples were obtained from 2 different segments of the same lobe or 2 different lobes, depending on the pre-procedural planning.

The patient was extubated immediately after the procedure and observed for 2 hours. After this period, a chest X-ray was obtained before discharge. A nurse followed up with each patient 48 hours later to evaluate the presence of any new respiratory symptoms.

Data were described using absolute and relative frequencies (percentage) or position indices (mean or median) and relative dispersion indices (SD or interquartile range), as appropriate according to the type and distribution of the variable analyzed. Sensitivity and accuracy were calculated for the study procedure with regard to final diagnosis.

3. Results

Among the 11 patients included in the study, 3 (27.3%) were females, and the median age was 59.0 ± 26.5 years. There were no missing data among the variables of interest (Table 1). The median diffusing capacity for carbon monoxide as a percentage of predicted was 52 ± 14, obtained within 15 ± 8 days before the TBCB procedure. In 1 case, the procedure was repeated twice due to an inconclusive result in the first attempt. The median number of biopsy samples obtained per patient in a single procedure was 2.0 ± 0.5, with a median diameter of 5 ± 0.5 mm.

Table 1 presents the suspected diseases, the number of biopsies obtained per segment, and the final pathological diagnosis for each patient. TBCB resulted in a definitive histological diagnosis in 9 out of 10 cases during the initial procedure, yielding a sensitivity and accuracy of 90.1%. When including the second procedure, required in 1 case, the sensitivity and

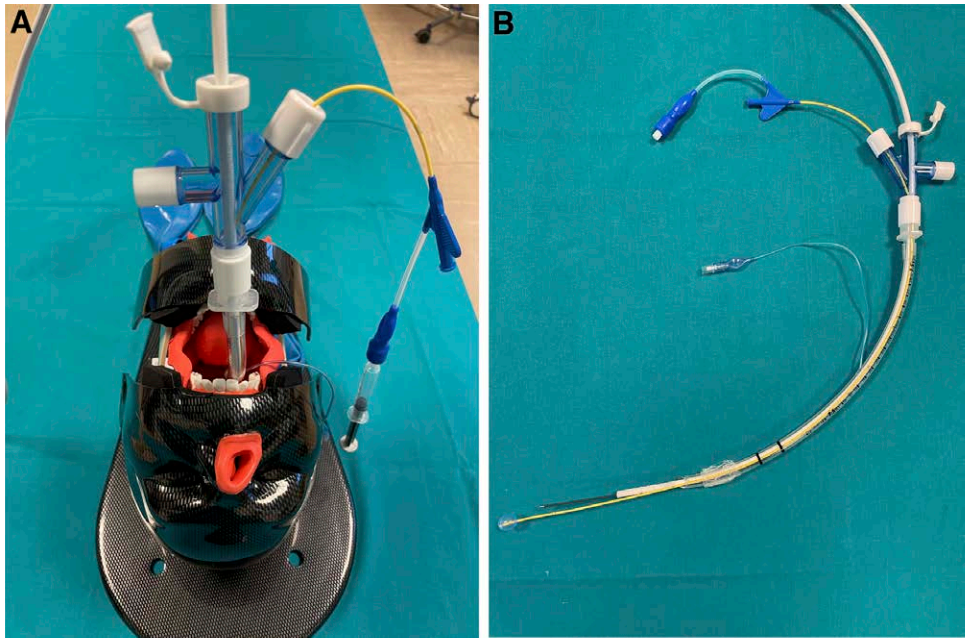

Figure 1. Setup used for transbronchial cryobiopsy. The patient is intubated with a 7.5 mm endotracheal tube, keeping the cuff deflated to allow maintenance of spontaneous breathing (panels A, B). A 5 Fr endobronchial blocker is introduced through a proprietary Y junction which locks it to the endotracheal tube (panel B). The bronchoscope enters the endotracheal tube from an independent channel of the Y junction (panels A, B).

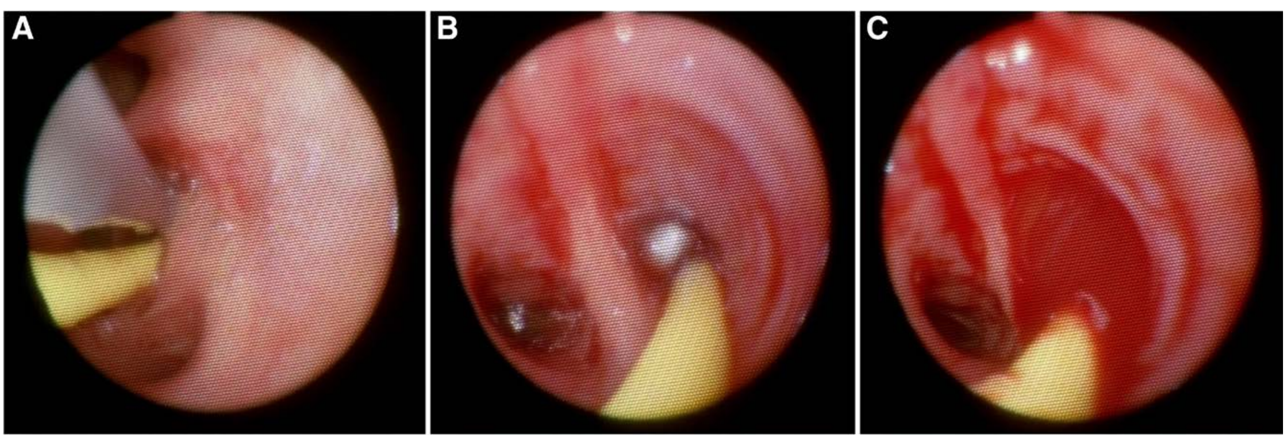

Figure 2. Steps of the proposed technique for transbronchial cryobiopsy. The deflated endobronchial blocker is placed at the entrance of the selected segmental bronchus, and a 1.7 mm cryoprobe is introduced in the same bronchus (panel A). After cryobiopsy, the bronchoscope and the cryoprobe are removed en-block from the endotracheal tube and the endobronchial blocker balloon is immediately inflated (panel B). The bronchoscope is reinserted, and the balloon is deflated to assess potential bleeding (panel C).

accuracy increased to 90.9%. In all cases, there was concordance between the histological diagnosis and the final clinical diagnosis.

The median amount of sedation required was 7.0 ± 1.4 mg of midazolam and 100.0 ± 50.0 mcg of fentanyl. Three out of 12 procedures (25.0%) required the application of continuous positive pressure immediately after placing the ETT, while the remaining 9 cases maintained a $SpO_2 > 90\%$ under HFNC. The median duration of the procedure was 18 ± 7 minutes after achieving optimal sedation.

Minor and self-limiting bleedings occurred in 4 out of 12 procedures (33.3%). In 4 cases (33.3%), hemostatic tamponade and local instillation of cold saline, tranexamic acid, and/or epinephrine were necessary to stop moderate bleedings. Four patients (33.3%) experienced more severe bleedings, requiring reinflation of the EBB to arrest.

The incidence of pneumothorax was 2/12 (16.6%). Both patients reported the onset of chest pain after the procedure and in both cases a complete pneumothorax (maximum thickness 2.5 and 5 cm, respectively) requiring drainage was confirmed at the chest X-ray.

No other complications occurred during the procedures or during the observation periods. All patients but those with pneumothorax were discharged 2 hours after the TBCB, and none of them reported the onset of new symptoms during a subsequent telephone follow-up at 48 hours. The 2 patients who required drainage of the pneumothorax were discharged after 24 and 48 hours, respectively.

4. Discussion

We introduced a novel technique for performing TBCB during a flexible bronchoscopy session, without the need for anesthesiologic assistance. Compared to traditional rigid bronchoscopy, our approach offers significant advantages, including shorter pre-procedural, procedural, and recovery times, which result in

Table 1

Baseline and procedural details.

Patient n.	Age, yrs	Sex	Suspected disease	TBCBs, total n.	Sampled segments	Specimen size, mm[a]	Sedation (midazolam, mg; fentanyl, mcg)	Respiratory support, FiO_2 (%)[b]	Complications	Histological diagnosis	Final diagnosis
1	74	M	Lepidic ADK	2	RB9, RB10	5	4.5; 50	HFNC, 60%	Mild bleeding	Lepidic ADK	Lepidic ADK
2	73	M	IPF	2	RB9, RB10	4	12; 100	HFNC, 60%	Moderate bleeding	UIP	IPF
3	39	M	Sarcoidosis	2	RB8, RB9	5	8; 50	CPAP, 60%	Moderate bleeding	Inconclusive	Inconclusive
3, 2nd procedure	39	M	Sarcoidosis	2	LB9, LB10	6	7; 50	HFNC, 60%	Moderate bleeding	Noncaseating granulomas	Sarcoidosis
4	58	F	Miliary TB	3	RB8, RB9, RB10	5	6; 100	HFNC, 80%	None	Caseating granulomas	Miliary TB
5	73	F	COP	2	LB2, LB3	5	3.5; 30	CPAP, 100%	Severe bleeding	Organizing pneumonia	COP
6	77	M	IPF	2	RB9, RB10	6	6; 40	HFNC, 50%	Moderate bleeding	UIP	IPF
7	60	M	PVOD	3	LB9, LB10	4.5	7; 200	CPAP, 80%	None	PVOD	PVOD
8	63	M	HP/IPF	2	RB8, RB10	5	4; 100	HFNC, 60%	Severe bleeding	HP	HP
9	37	M	Sarcoidosis	2	LB9, LB10	5	7; 100	HFNC, 60%	PNX	Lymphoid infiltrates, granulomas	GLILD
10	63	M	Organizing pneumonia	2	RB9, RB10	19.5	7; 100	HFNC, 60%	Severe bleeding	Organizing pneumonia	Amiodarone pneumonitis
11	46	F	Rituximab pneumonitis	2	LB9, LB10	5	7; 100	HFNC, 60%	PNX	NSIP	Rituximab pneumonitis

ADK = adenocarcinoma, COP = cryptogenic organizing pneumonia, CPAP = continuous positive airway pressure, F = female, FiO_2 = fraction of inspired oxygen, GLILD = granulomatous-lymphocytic interstitial lung disease, HFNC = high-flow nasal cannula, HP = hypersensitivity pneumonitis, IPF = idiopathic pulmonary fibrosis, M = male, NSIP = nonspecific interstitial pneumonitis, PNX = pneumothorax, PVOD = pulmonary veno-occlusive disease, TB = tuberculosis, TBCB = transbronchial lung cryobiopsies, UIP = usual interstitial pneumonia.

[a]Mean size of the samples.

[b]Highest-intensity respiratory support required during the procedure (CPAP refers to continuous positive airway pressure delivered through the endotracheal tube with deflated cuff).

a higher cost-effectiveness profile.[12] Indeed, all procedures were conducted in an endoscopy suite, allowing patients to be treated as outpatients and discharged shortly after observation.

From a technical perspective, the use of an ETT enabled rapid and repeated access to the airways with the bronchoscope, while the EBB protected the bronchi from a potential massive bleeding.[19] In the event of a hemorrhage, the patient being already intubated enhances the safety of the technique, making it comparable to commonly recommended approaches, such as rigid bronchoscopy.

We successfully managed 4 cases of moderate bleeding and 4 cases of more severe bleeding without further complications. Although the rate of moderate and severe bleeding was higher than reported in the literature, we emphasize that it might have been overestimated due to the small sample size; and the quantification of bleeding is subjective, leading to variability between studies.[20,21] The incidence of pneumothorax was in agreement with the existing literature that recommends using a 1.7 mm cryoprobe, fluoroscopic guidance, and maintaining a 2 cm sampling distance from the pleura.[20,22] TBCB was feasible in all cases, and no other procedural complications were observed.

The median size of the biopsy specimens was non-inferior to what reported in the literature for the traditional TBCB techniques, and in 1 case a large (35 mm) sample was obtained.[5,6]

The diagnostic yield achieved in the first procedure was 90.1%, mostly aligning with available data.[15,16,21,23] We believe the inconclusive histological response obtained in 1 case was mainly due to the choice of biopsy site rather than the technique itself. In this single case, we successfully repeated TBCB despite current guidelines suggest considering SLB if TBCB results are nondiagnostic.[10,20] Therefore, it is possible that a faster, cheaper, and safer technique might orient towards a recommendation for repeated TBCB in the future.

Four patients required additional respiratory support with CPAP, probably due to a smaller tracheal lumen resulting in lower air leaks around the uncuffed ETT. Nevertheless, all patients maintained a completely spontaneous breathing pattern, and no anesthesiologic complexities or the need for invasive mechanical ventilation were encountered. Although we have not encountered any patients unable to undergo the procedure, there may be some who cannot tolerate intubation under conscious sedation. We believe that these patients can be identified during the early phases of the procedure, allowing it to be interrupted before the occurrence of further complications. However, we cannot exclude that cough can appear during or after sampling, causing the proceduralist to have less confidence especially in case of bleeding. However, the balloon blocker we used can be secured in place through a proprietary threaded locking system (Fig. 1), preventing cough-induced disruptions in positioning and thus ensuring a high level of safety. Even if, our experience, we did not experience major procedural complexities also in case of severe bleeding requiring inflation of the balloon for several minutes, our results should be confirmed in larger cohorts.

Other authors have reported alternative techniques for TBCB. Sharma et al assessed the effectiveness and safety of TBCB performed under conscious sedation, using a flexible bronchoscope and an EBB, but not an artificial airway nor fluoroscopy. On 100 procedures, the Authors experienced a diagnostic yield of 82% and a similar rate of complications compared to our data (i.e. pneumothorax 13%, mild bleeding 58%, moderate bleeding 20%).[24] O'Mahony and colleagues performed TBCB with the same technique, reporting a lower diagnostic yield (67%) but a consistent safety profile.[16] Another retrospective study reported a 9.3% 30-day mortality in patients who underwent TBCB either without intubation and EBB positioning in the endoscopy suite or under general anesthesia through an ETT in the ICU.[17] However, this study included critical ICU inpatients and utilized both 1.9 and 2.4 mm probes, with the latter associated with a higher complication rate.[22] On the contrary, a lower incidence of pneumothorax (4%) has been described using an ultrathin 1.1 mm cryoprobe and retrieving the specimens through the working channel of the bronchoscope.[25,26] Oki et al[18] positioned a nasotracheal cannula to facilitate bronchoscope access after TBCB. However, a prophylactic balloon was not used, contrary to current recommendations.[15] Differently, Bango-Álvarez et al[27] employed 2 flexible bronchoscopes simultaneously in a cohort of 106 patients under moderate sedation, without endotracheal intubation and fluoroscopy guidance.

Our study is preliminary, mainly due to the limited number of procedures performed which may have led to an underestimation of complication incidences. Although we believe that our technique is more cost-effective than guideline suggested ones due to reduced personnel requirement, shorter pre-procedural and post-procedural periods, more accessible equipment, and no need for hospitalization, we did not perform a comparison of real costs. Before it can be recommended for routine use, further large-scale studies are required to compare our technique with traditional approaches, standardize the procedure, and address key considerations, such as ideal sedation, respiratory support, and ETT diameter.

In conclusion, our proposed technique can enhance the accessibility and feasibility of TBCB even in centers without access to anesthesiologic assistance, reducing the time and costs of the procedure while maintaining a high safety profile. Larger, randomized, studies will be required to validate and refine our findings.

Author contributions

Conceptualization: Francesco Salton, Marco Biolo, Liliana Trotta, Marco Confalonieri.
Data curation: Francesco Salton, Marco Biolo, Liliana Trotta, Lucrezia Mondini, Alessia Giovanna Andrisano, Paola Confalonieri, Caterina Antonaglia, Marco Confalonieri, Barbara Ruaro.
Formal analysis: Francesco Salton, Liliana Trotta, Caterina Antonaglia.
Investigation: Francesco Salton, Lucrezia Mondini, Alessia Giovanna Andrisano, Paola Confalonieri.
Methodology: Francesco Salton, Lucrezia Mondini, Alessia Giovanna Andrisano, Nicolò Reccardini, Paola Confalonieri, Marco Confalonieri.
Validation: Francesco Salton, Lucrezia Mondini, Alessia Giovanna Andrisano, Nicolò Reccardini, Paola Confalonieri, Barbara Ruaro.
Writing – original draft: Francesco Salton, Marco Biolo, Liliana Trotta, Lucrezia Mondini, Alessia Giovanna Andrisano, Nicolò Reccardini, Barbara Ruaro.
Writing – review & editing: Francesco Salton, Marco Biolo, Nicolò Reccardini, Caterina Antonaglia, Marco Confalonieri, Barbara Ruaro.
Supervision: Marco Biolo, Paola Confalonieri, Caterina Antonaglia, Marco Confalonieri, Barbara Ruaro.
Visualization: Liliana Trotta, Lucrezia Mondini, Alessia Giovanna Andrisano, Nicolò Reccardini, Paola Confalonieri, Caterina Antonaglia, Barbara Ruaro.

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