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Prevalence and short-term outcomes of acute complications of tuberculosis: a cross-sectional, monocentre, Italian study

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Abstract

Background Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. Acute complications may impact on disease progression but their prevalence is unclear and prognostic outcomes of complicated patients have been poorly studied. The aim of the study was to estimate the prevalence of acute complications of TB at the time of diagnosis. Short-term outcomes were also evaluated.

Methods A cross-sectional study was carried out in Milan (Italy), from January 2018 to December 2023.

Results 201 patients with TB were recruited. 88 complications were recorded in 65 (32.3%) patients. Disseminated TB was the most frequent complication (30, 34.1%) followed by acute respiratory failure (23, 26.1%) and pleural empyema (6, 6.8%). In-hospital and 30-days mortality in complicated patients were 9/65 (13.8%) and 10/65 (15.4%), respectively. In-hospital mortality was significantly higher in patients with > 1 *versus* (VS) 1 complication (6, 31.6% VS 3, 6.5%, $p = 0.02$) without any difference in 1-month mortality (6, 31.6% VS 4, 9.8%, $p = 0.06$) between subgroups. Acute respiratory failure was the most lethal complication.

Conclusions The study shows a substantial rate of complications in patients with a new diagnosis of TB associated to a significant short-term mortality. A prompt screen of complications at diagnosis is needed to improve short-term outcomes of these patients.

Keywords Tuberculosis, Complication, Empyema, Disseminated TB, Respiratory failure, Miliary

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Introduction

Although tuberculosis (TB) is a preventable disease, it is a major cause of morbidity and one of the leading causes of death worldwide. Until the coronavirus disease 2019 (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent [1, 2].

TB most commonly manifests as a pulmonary subacute or chronic disease but acute clinical manifestations may occur and all organs may be potentially affected [3, 4].

Limited data on acute complication of TB can be found in the literature. They may significantly impact on disease progression and prognostic outcomes [3, 4].

Acute complications may be potentially life-threatening. They may show a rapid progression requiring intensive care unit (ICU) admission with a high mortality rate and/or development of severe post-acute infection sequelae [3–5]. The presence of comorbidities (e.g. human immunodeficiency virus, HIV infection or diabetes), exposure to immunosuppressive medications, and diagnostic delay may increase the risk of acute complications and negative outcomes [3–5].

Several pulmonary and extrapulmonary acute complications have been reported in the literature [3, 4, 6]. Respiratory failure related to extensive lung disease/acute respiratory distress syndrome (ARDS), pneumothorax, and life-threatening haemoptysis have been described as the most frequent complications of pulmonary TB [3–5]. Disseminated TB is the most severe complicated form while complications of meningitis (e.g., coma) and abdominal TB (e.g., intestinal perforation/obstruction) are the most studied extrapulmonary complications [3, 4, 6–9].

Early detection of complications and assessment of their frequency may help start prompt treatment.

Several studies reported a 13-86.8% incidence of long-term post-TB treatment complications, i.e. airflow obstruction, restriction, bronchiectasis, and respiratory infections [10, 11].

However, the prevalence of acute complications of disease is still unclear and prognostic outcomes of TB patients experiencing complications were poorly studied.

During COVID-19 pandemic, a decreased incidence of TB was recorded, following social distancing, long-term implementation of community-based restrictive lockdown measures, and a reduction of the healthcare activities of TB services worldwide [12–14]. However, an increased prevalence of disseminated forms was reported during the pandemic [15].

The aim of the present study was to estimate the prevalence of acute complications of TB at the first clinical presentation.

Prevalence of complications during pre-COVID-19 pandemic *versus* pandemic years were compared.

Rate of ICU admission, in-hospital case-fatality, and other short-term outcomes were also evaluated.

Methods

Study design

A cross-sectional, single centre study was carried out in Italy after the approval of the local ethical committee (approval number 3119/23). Outcomes were retrospectively collected.

Written informed consent was signed by all recruited patients. Data were collected from patients' medical charts.

Patients and interventions

From January 2018 to December 2023 adult (i.e., ≥18 years old) patients with a new diagnosis of TB or a TB relapse (both reactivation and reinfection) occurring after adequate treatment at ASST Santi Paolo e Carlo of Milan (Italy) were enrolled. Patients had the first diagnosis of TB or TB relapse after hospital admission.

TB diagnosis relied on clinical, radiological, and bacteriological (i.e., positive culture for *Mycobacterium tuberculosis* and/or nucleic acid amplification tests -polymerase chain reaction, PCR and/or Xpert MTB/RIF-) findings [16, 17]. Patients with a clinical diagnosis without any bacteriological confirmation were excluded (Fig. 1, supplementary file).

Patients who refused/were not able to sign the informed consent for the study participation were excluded.

Demographic and clinical data at the presentation and short-term outcomes were recorded. Acute disease complications, i.e. unfavourable and rapidly developing manifestations of the acute disease requiring a prompt specific management, were considered at the time of TB diagnosis before starting pharmacological therapies and were categorized according to the scientific literature [4, 6–8, 18–21]. In this study, disseminated TB was included in the list of complications [4, 7]. Adverse events of pharmacological treatments were not included.

In particular, disseminated TB was defined as an infection involving bloodstream, bone marrow, liver, or ≥2 non-contiguous organs [6–8]. Miliary TB is a form of disseminated TB [4, 6–8, 18].

Spinal TB was deemed complicated only if needing surgical intervention, including drainage of the abscess, debridement of infected tissues, stabilization of vertebrae, and deformity correction [20, 21].

Life-threatening haemoptysis was defined as any haemoptysis with an estimated blood loss > 100 ml/24 hours or causing hemodynamic instability, or inducing an alteration of gas exchange and/or airway obstruction [22].

Outcomes

The primary outcome was to estimate the prevalence of acute complications during the study period at the time of the disease diagnosis and before starting pharmacological treatment.

Furthermore, prevalence of patients with complications, number and type of complications, and their targeted therapy were described.

Prevalence of acute complications between patients at the first diagnosis *versus* (VS.) relapse, and between pre-COVID19 pandemic (i.e. 2018–2019) VS. pandemic years (2020–2023) were compared.

ICU admission rate, in-hospital case-fatality, 30-day case-fatality, and complication relapse within 30 days from admission were also recorded. The rate of lethality for each complication was also assessed.

Statistical analysis

Qualitative and quantitative variables were summarized with absolute and relative (percentage) frequencies and means (standard deviations) or medians (interquartile ranges) depending on their normal distribution, respectively. Prevalence of complications was calculated and reported with its 95% Confidence Intervals (CI). Chi-squared or Fisher exact tests were adopted for the comparison of qualitative variables, whereas student t or Mann-Whitney test for normally and non-normally distributed variables, respectively. A P less than 0.05 was considered statistically significant. Stata version 17 was the software adopted for all statistical computations.

Results

A total of 201 (133 (66.2%) males) patients with a median (IQR) age of 43.5 (30-61.5) years with a diagnosis of TB were recruited during the study period. 187 (93%) had a new disease whereas in 14 (7.0%) a relapse was diagnosed; in the majority of the cases (12, 85.7%) it was the first relapse episode. The majority of the diagnoses (177, 88%) were performed in patients admitted to the emergency department, whereas the remaining (24, 12%) in outpatient settings. Clinical and demographic characteristics are described in the Table 1.

189/201 (94%) were hospitalized after diagnosis. None died before treatment initiation.

Overall, a total of 88 complications (43.8%; CI: 36.9-50.6%) were observed: 65 (32.3%; CI: 25.9-38.8%) experienced one, 20 (9.9%; CI: 5.8-14.1%) two, and 3 (1.5%; CI: 0.5-3.17%) three complications, respectively. Patients with complications were older and had a higher prevalence of chronic renal and heart failure than those without.

Overall, disseminated TB accounted for 14.9% of all cases and was the most frequent complication (30/88, 34.1% followed by acute respiratory failure caused by extensive lung disease (23/88, 34.1%) and pleural empyema (6/88, 6.8%) (Table 2; Fig. 1). Two patients with life-threatening haemoptysis and one with tension pneumothorax developed secondary, transient, respiratory failure and were treated with oxygen therapy.

TB therapy was started after a median (IQR) of 4 (2–11) days from the hospital admission whereas treatment of complications immediately after their diagnosis.

Supplemental oxygen therapy (23 (35.4%) patients with respiratory failure), chest tube placement with/without intrapleural fibrinolytics (4 (6.1%) pleural empyema and 2 (3.1%) pneumothorax) and intravenous tranexamic acid administration (5 (7.3%) with life-threatening haemoptysis) were the interventions most frequently prescribed (Table 3).

There was no statistically significant difference in the prevalence of acute complications between patients at the first diagnosis of TB VS. relapse (62/188, 33% Vs 3/13, 23.1%; P: 0.34).

The number of patients with ≥ 1 complications did not differ between the pre-COVID19-pandemic (i.e. 2018–2019) VS. pandemic years (2020–2023) (23, 28.7% VS. 42, 34.7% respectively; P: 0.38).

5/65 (7.7%) patients with complications (3 with ARDS, 1 with a disseminated TB and pneumothorax, and 1 with a pleural empyema and a spondylodiscitis) were admitted to ICU resulting in an ICU mortality of 40% (2/5).

Overall, 11/201 (5.5%; CI: 3.0-9.6%) patients died during their hospital stay and deaths were attributed to a TB complication in 9/11 (81.8%) patients. The remaining 2/11 (18.1%) patients died for a bacterial pneumonia and a sudden cardiac arrest.

The median duration of hospitalization of the patients who died was 17 (IQR: 14–28) days.

The overall 30-day mortality was 6.9% (CI: 4.0-11.7%) (12/175) and death was attributed to a complication of disease in 10/12 (83.3%) patients (Table 3) (Fig. 2, supplementary file).

In-hospital and 30-day mortality in patients experiencing at least one complication was 13.8% (9/65) and 15.4% (10/65), respectively. In-hospital mortality was significantly higher in patients with > 1 complication than with only 1 complication (6/20, 30% VS. 3/45, 6.5%; P: 0.02), without any differences in 1-month mortality between subgroups (6/20, 30% VS. 4/45, 8.8%; P: 0.06). None died before treatment initiation.

Complications most frequently related to in-hospital death were acute respiratory failure (8, 53.3%) and disseminated TB (4, 44%) (Table 3).

45 (69.2%) patients recovered from complications during hospitalisation. No patients experienced a complication relapse within 30 days from admission.

Table 1 Clinical and demographic characteristics of the enrolled patients related to the presence of complications

		Patients without complications *N* = 136	Patients with complications *N* = 65	*p*-value
Median (IQR), Age		40 (29–57)	49 (31.0–65.0)	0.02
Male, n (%)		96 (70.6%)	37(56.9%)	0.06
Median (IQR) BMI		21.3 (18-8-24.0)	20.8 (19.6–23.4)	0.60
Ethnicity, n (%)	Caucasian	62 (45.9)	33 (50.8)	0.59
	Hispanic	21 (15.6)	6 (9.2)	
	Asian	30 (22.2)	13 (20.0)	
	African	22 (16.3)	13 (20.0)	
Smoking history, n (%)	Never smoker	26/58 (44.8)	9/29 (31.0)	0.21
	Former smoker	5/58 (8.6)	6/29 (20.7)	
	Active smoker	27/58 (46.6)	14/29 (48.3)	
Pack/years	Mean (SD)	44 (38.8)	26.1 (23.4)	0.29
Tuberculosis (disease status at diagnosis), n (%)	First episode	126 (92.6)	62 (95.4)	0.46
	Relapse	10 (7.4)	3 (4.6)	
Tuberculosis (pharmacological resistance), n (%)	Sensitive	128 (94.1)	61 (93.9)	0.33
	Mono-resistant 1	4 (2.9)	2 (3.1)	
	RR	1 (0.07)	0 (0.0)	
	XDR	0 (0.0)	1 (1.5)	
	MDR	0 (0)	1 (1.5)	
	Dual mono-resistance	3 (2.2)	0 (0.0)	
HIV, n (%)		6/131 (4.6)	5/63 (7.9)	0.34
Haematological malignancy, n (%)		1/131 (0.7)	3/63 (4.65)	0.10
Solid malignancy, n (%)		6/131 (4.4%)	2/63 (3.1%)	1.00
Autoimmune diseases, n (%)		2/131 (1.5%)	2/63 (3.1%)	0.59
Chronic renal failure, n (%)		3/131 (2.2)	7/63 (10.8)	0.01
Diabetes mellitus, n (%)		17/131 (12.5)	6/63 (9.4)	0.52
Chronic liver disease, n (%)		4/131 (4.4)	7/63 (10.9)	0.12
Chronic lung disease, n (%)		11/131 (8.1)	11/63 (16.9)	0.09
Chronic heart disease, n (%)		8/131 (12.9)	11/63 (16.9)	0.02
Immunomodulatory therapy (i.e. corticosteroids, immunosuppressants; chemotherapy) > 1 month, n (%)		3/131 (2.2%)	5/63 (7.8%)	0.06

BMI: body mass index; DS: drug sensitive; RR: rifampin resistant; MDR: multidrug resistant; XDR: extended drug resistant; HIV: human immunodeficiency virus

Discussion

To the best of our knowledge, this is the first study aimed at describing the prevalence of acute complications in patients with TB at the diagnosis. Limited data related to low TB incidence countries can be found in the literature.

Our data, collected at a single centre in Italy, show a substantial rate of complicated forms with 32% of newly diagnosed patients experiencing at least one complication, without any differences between the prevalence at the first diagnosis and at the disease relapse.

Despite an immediate pharmacological and non-pharmacological therapy after the first hospital admission, complicated TB was associated with a high in-hospital and 30-day mortality, with patients with > 1 complication showing a significantly higher risk of death.

Overall, our results suggest that prompt screening for complications at the diagnosis is highly recommended, especially for disseminated TB and respiratory failure, which are most frequently associated with a high mortality. An early detection might reduce the probability of poor short-term outcomes.

Our study showed a higher case-fatality ratio than that reported in other European low-incidence countries, which showed a lethality of 1.6–6.6% [23–26]. However, they described long-term prognostic outcomes. Interestingly, in the study by Holden et al., half of deaths occurred within the first month after diagnosis [26].

Despite a decrease in TB diagnoses worldwide during the COVID-19 pandemic [12–14], no differences were found in the prevalence of complicated forms of TB before and during the COVID-19 pandemic. Similar complication rates before and during the pandemic might suggest the resilience of our healthcare system.

Our findings are in contrast with Barrett et al. who demonstrated an increased prevalence of disseminated TB during the pandemic [15]. However, their findings were only related to this specific complication of disease.

Table 2 Characteristics of complications and their targeted treatment

		N **= 201**	Treatment of complication	***N*** (%)
Patients with complications, *n* (%)		65 (32.3)		
Complication		***N*** **= 88**		
Complication, *n* (%)	Disseminated tuberculosis	30 (34.1)		
	Miliary TB	18		
	Other	12		
	Acute respiratory failure related to extensive lung disease	23 (26.1)	Supplemental oxygen therapy	23
		13	Non-invasive mechanical ventilation	(100)
	Pneumonia	7	Invasive mechanical ventilation	3 (13.0)
	Miliary TB	3		3 (13.0)
	ARDS			
	Pleural empyema	6 (6.8)	Chest tube and intrapleural fibrinolytics	4 (66.7)
			Medical thoracoscopy	2 (33.3)
			Surgical thoracoscopy/VATS	2 (33.3)
	Life-threatening haemoptysis	5 (5.7)	Bronchial artery embolization	3 (60.0)
			Tranexamic acid intravenous administration	5 (100)
			Blood transfusion	1 (20.0)
			Vasopressor medications	1 (20.0)
	SIADH	4 (4.5)	Water restriction and/or administration of hypertonic solution	2 (50.0)
	Pulmonary embolism	4 (4.5)	Anticoagulation	3 (75.0)
	Complicated spondylodiscitis	3 (3.4)	Neurosurgery	3 (100)
	Miscarriage/fetal complications	3 (3.4)	Abdominal/Gynecological surgery	2 (66.7)
	Pneumothorax	2 (2.3)	Chest tube	2 (100)
	Brain stroke	2 (2.3)	Supportive medical care	2 (100)
	Cardiac tamponade	1 (1.1)	Corticosteroids and supportive medical care	1 (100)
	Cerebral oedema	1 (1.1)	Hyperosmolar agent (mannitol)	1 (100)
	Hydronephrosis	1 (1.1)	Abdominal surgery (nephrectomy)	1 (100)
	Gastrointestinal perforation	1 (1.1)	Abdominal surgery	1 (100)
	Intestinal occlusion	1 (1.1)	Abdominal surgery	1 (100)
	Gastrointestinal haemorrhage	1 (1.1)	Blood transfusion	1 (100)*

* Patient not eligible for surgery

TB: tuberculosis; ARDS: acute respiratory distress syndrome; VATS: video-assisted thoracoscopic surgery; SIADH: syndrome of inappropriate antidiuretic hormone secretion

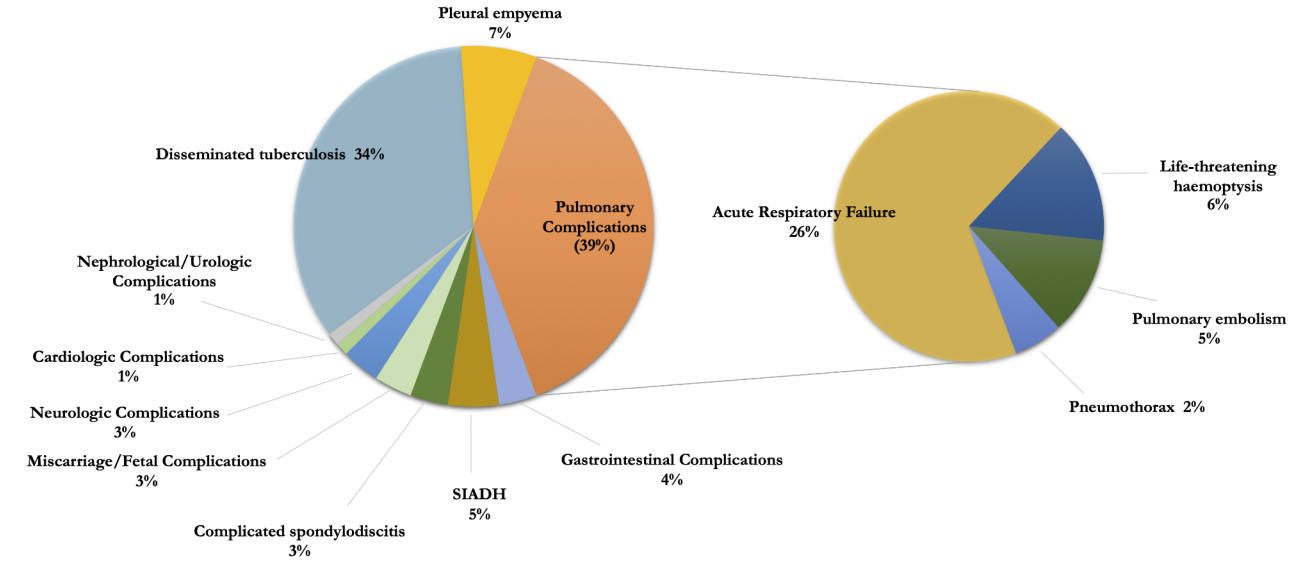

Fig. 1 Distribution of TB complication

Table 3 In-hospital and 30-days case-fatality ratio of complicated tuberculosis

Total deaths in patients experiencing at least one complication, *n* (%)	**In-hospital: 9/65 (13.8)***	**30-days: 10/65 (15.4)***
Complication (*n*)	**In-hospital mortality, *n* (%)***	**30-days mortality, *n* (%)***
Acute respiratory failure (23)	8/23 (34.8)	9/23 (39.1)
Disseminated tuberculosis (30)	4/30 (13.3)	4/30 (13.3)
Complicated spondylodiscitis (3)	1/3 (33.3)	1/3 (33.3)
Pulmonary embolism (4)	1/4 (25)	1/4 (25)
Gastrointestinal haemorrhage (1)	1/1 (100)	1/1 (100)
Intestinal obstruction (1)	1/1 (100)	1/1 (100)

*Patients who died could have had more than one complication

Disseminated TB, which was diagnosed in 14.9% of the enrolled patients, was the most frequent complication in our study and was associated with a high mortality rate. Our rate was slightly lower than those described in the literature (i.e., 15.8–23.7%) [8, 15]. However, we recorded a higher 1-month mortality rate (33%) than that reported by Crump et al. (21%) who described a group of disseminated TB patients from 1980 to 1999 [8] A higher rate of miliary TB, a lethal form of disseminated disease, was recorded in our study [4, 8].

Overall, in all patients admitted to ICU a mortality of 40% was recorded, confirming findings of previous studies.

Respiratory failure due to extensive lung disease was the second most frequent complication, the most frequent cause of ICU admission, and was associated with the highest mortality.

These findings, which are consistent with the scientific literature [4, 5, 27], are of particular relevance considering that prompt pharmacological therapy and complication management (i.e., oxygen and mechanical ventilation) was implemented in all patients.

Tuberculous pleural effusions represent a common form of extrapulmonary TB [3, 6, 28]. However, pleural empyema is a rare entity which usually represents a complication of primary tuberculous pleurisy [3, 28]. A complete recovery with good short-term outcomes was described in all individuals enrolled in our study, despite the requirement for invasive procedures. However, possible residual pleural thickening inducing long-term respiratory functional impairment was described [3, 28].

TB is an uncommon cause of haemoptysis in Europe and if occurs, it is usually mild [3, 29]. Cases of potentially life-threatening haemoptysis described in our study were immediately detected and successfully treated with drugs and bronchial artery embolization without any relapse and death.

Female genital TB is a rare form of extrapulmonary TB in Europe, but a common cause of infertility in countries with a high TB incidence [3, 6, 30, 31]. Interestingly, three cases of complicated female genital TB (two in a disseminated form) were described in our study. Two were associated with a miscarriage and one with an emergency C-section for fetal distress. Our study has some limitations.

The monocentric design of the study is the main limitation to the inference. Furthermore, the relatively small sample size and the likely poor statistical power might explain some non-significant results. Thus, final conclusions might be misleading.

The majority of the patients had drug-susceptible disease. Thus, our findings are not representative of all TB cases worldwide. Furthermore, the majority of the diagnoses were performed in patients admitted to the emergency room and, therefore, the rate of severe acute complications might be overestimated. The short follow-up period and the formal absence of the analysis of risk factors hinder the description of long-term outcomes and of the main predictors of TB complications.

Absence of information on the time between symptom onset and diagnosis does not help understand if a diagnostic delay could play a role in the high prevalence of complications.

In conclusion, our study showed a substantial rate of complications in patients with a new diagnosis of TB. Despite a rapid diagnosis and an immediate therapy, complicated TB was associated with a high short-term mortality, with patients with >1 complication showing a significantly higher risk of death.

Prompt screening for complications at the time of diagnosis is recommended to implement targeted interventions and improve short-term outcomes.

Future studies are needed to identify the main variables associated with complications and assess long-term outcomes of patients surviving acute complications.

Abbreviations

COVID-19	Coronavirus disease 2019
TB	Tuberculosis
ICU	Intensive care unit
HIV	Human immunodeficiency virus
ARDS	Acute respiratory distress syndrome
PCR	Polymerase chain reaction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10892-9.

Supplementary Figure 1: Study flow-chart

Supplementary Figure 2: Kaplan–Meier curves for overall survival at 30 days, related to the presence of complications

Author contributions

Authorship: MM: conception and design; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted. CA: conception and design and acquisition of data; drafting

the article and revising it critically for important intellectual content; final approval of the version to be submitted. ST: acquisition of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted. MP: analysis and interpretation of data; revising it critically for important intellectual content; final approval of the version to be submitted. SM: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. GF: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. SH: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. OV: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. AS: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. GM: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. SC: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted. CCD: analysis and interpretation of data; revising it critically for important intellectual content; final approval of the version to be submitted. GS: conception and design and analysis and interpretation of data; revising it critically for important intellectual content; final approval of the version to be submitted.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Approval was obtained from the ethics committee of Lombardia 1 (Milan, Italy; approval number 3119/23). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Clinical trial
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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