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Italian multicentre study on the management of pLeural infection and empyema: IMPLE study

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Abstract

Introduction Pleural infection is a significant global healthcare challenge. While medical thoracoscopy (MT) is well-established for undiagnosed or malignant pleural effusion, its effectiveness in management of pleural infection lacks robust evidence. Moreover, data on the optimal timing of intervention in pleural infection are still scarce.

Objective To assess the probability of subsequent surgical referral in adult hospitalized patients with stage 2-3 pleural infection/empyema according to type and time of first procedures accounting for confounders.

Methods We conducted a multi-centre observational study. We retrospectively collected baseline demographic and clinical characteristics, RAPID score, type and time of first-line intervention. We evaluated their impact on probability of surgical referral, length of hospital stay (LOS) and 90-day mortality using multivariable logistic/multiple quantile regression models.

Results We included 509 patients from 14 Italian centres (75.4% male, median (interquartile range) age 63 (49-76) years). Thoracentesis and chest tube placement were associated with a significant higher probability of subsequent surgical referral compared to MT (OR 6.0, 95% CI 1.8-20.6, p=0.004; OR 7.8, 95% CI 2.6-22.5, p<0.001, respectively). Additionally, chest drain insertion and upfront surgery were related to a longer LOS compared to MT (Regression Coefficient Estimates: 4.9; 95% CI 1.5-8.4; 5.2; 95% CI 1.0-9.5, respectively). Furthermore, a delayed intervention, regardless of type, resulted in a longer LOS.

Conclusion Our large real-world study provides valuable insights into management and outcomes of pleural infection, revealing different approaches among centres and suggesting that a timely MT, when adopted as first-line intervention, could reduce the probability of subsequent surgical referral, However, further prospective studies are required to confirm these findings.

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Introduction

Pleural infection represents a significant challenge to health care systems worldwide, due to its substantial morbidity and mortality and the increasing burden over time [1–5].

Nevertheless, there is still no consensus on the optimal treatment. Pleural infection is typically managed with a combination of antibiotics and chest tube drainage plus intrapleural fibrinolytics, which are effective in the majority of cases. However, when these measures fail to achieve adequate source control, escalation to surgical intervention—most commonly video-assisted thoracoscopic surgery (VATS) or open thoracotomy—is considered the standard next step. Surgical referral is therefore a critical decision point in the management pathway, as it reflects both first line treatment failure and the need for more invasive options [6, 7].

Although medical thoracoscopy (MT) is a recognized essential procedure in diagnosis and management of malignant pleural effusion (MPE) [8], in Italy, MT is widely adopted also for draining (± adhesiolysis, ± irrigation) pleural infection [9, 10]. Moreover, it can represent a valuable diagnostic tool in less definite clinical scenario (e.g. pleural malignancy presenting with loculations) where pleural biopsies are required. Nevertheless, strong evidence supporting its use in pleural infection is still lacking. A recent meta-analysis reported a pooled treatment success rate of 85% in pleural infection when MT was used as first-line therapy or after failure of chest tube, with a complication rate of 9% [11], but included only retrospective case series.

The combined intrapleural administration of tissue plasminogen activator (tPA) and DNase in patients with pleural infection has also shown to reduce the frequency of surgical referral and the duration of the hospital stay in a large randomised controlled trial [12], but use of these medications is not widespread and standardised worldwide.

Moreover, a recent feasibility randomised controlled trial showed potential shortening of length of stay with early surgery [13], and further, although limited, data suggest that delay in starting any treatment approach can increase duration of hospital stay and mortality [14–16].

Therefore, we conducted this multi-centre retrospective observational study to assess the risk of surgical referral based on the type (i.e. MT vs. Thoracentesis vs. Chest drain) and time (< 24, 24–48, > 48 h) to first line procedure in adult hospitalized patients with stage 2–3 pleural infection (i.e. Stage 2: fibrinopurulent effusion; Stage 3: organising) [14] or empyema, defined as evidence of purulent fluid into pleural cavity [15]. We also aimed to describe their epidemiological, clinical, radiological, and serological characteristics and to estimate their hospital length of stay (LOS) and to assess the 90-day mortality according to the type (i.e. MT vs. Thoracentesis vs. Chest drain vs. Upfront surgery) and time (< 24, 24–48, > 48 h) to first-line management, accounting for demographics, number of comorbidities, and RAPID score.

Methods

Study design

This multi-centre observational retrospective study involved 14 tertiary Italian hospitals (see Supplementary Materials S1 for the complete list of centres).

Population

We retrospectively included patients with presumed community-acquired and hospital-acquired pleural infection and a diagnosis of stage 2–3 pleural infection or empyema [17] from 1 st January 2015 to 31 st December 2021.

Complicated pleural effusion (CPE) comprises stages 2–3 of pleural infection (i.e. stage 2: fibrinopurulent; stage 3: organising), being defined as a pleural effusion that met one or more of the following criteria: positive fluid microbiological Gram's stain or culture; pleural fluid pH < 7.2 plus supportive evidence for infection; presence of pleural septations or loculations in the context of an infective presentation [17].

Exclusion criteria were malignant pleural effusion, thoracic malignancy, traumatic empyema, iatrogenic and empyema, active pulmonary or pleural tuberculosis, history of previous pleurodesis, and pregnancy.

Data collection and ethical approval

We collected demographic, clinical, serological, and radiological characteristics of each enrolled patient from the day of hospitalization (i.e. start date) (See Supplementary Materials S1 for more details) with clinical outcome data through review of clinical records. The study was approved by Coordinator Centre Ethical Committee with the number 2022 – 129.

Consent to participate

Consent to participate was obtained from all participants during the general informed consent process, which included the information that de-identified clinical data could be used for research purposes. This ensured that all individuals agreed to the potential secondary use of their data, while maintaining full confidentiality and anonymity.

Consent to publish

Consent to publish of anonymized data was obtained from all participants during the general informed consent process, as above speciafied.

Clinical trial number
Not applicable.

Statistical analysis
Epidemiological, clinical, radiological, and serological characteristics of hospitalized patients were summarized as median and interquartile range (1st –- 3rd quartile, IQR) for quantitative variables or as absolute and percentage frequencies for qualitative variables.

Quantitative variables were compared using Kruskall-Wallis test, while qualitative variables were analysed using Chi-square test.

We estimated the independent effect of the type of first procedure (MT vs. Thoracentesis vs. Chest drain), the time to first intervention (< 24 h; 24–48 h; >48 h) and of baseline thoracic ultrasound (TUS) features (i.e. presence/absence of loculations/septations), on three outcomes of interest: subsequent surgical referral, 90-day mortality from hospital admission, and length of hospital stay. Multivariable logistic regression analysis was performed for the first two outcomes and results were reported as Odds Ratio (OR) and 95% Confidence Interval (95%CI); we used multiple linear quantile regression analysis to estimate the median value of LOS in days. Quantile regression is a non-parametric method which does not hold any assumption on the distribution of the dependent variable. It allows to estimate the effect of the independent variables on specific quantiles of the distribution of the dependent variable. Results were expressed as estimates of the regression coefficients and 95%CI and considered significant if 0 was not included in the interval.

All the statistical models were adjusted by RAPID score, number of comorbidities and age.

On the subgroup of patients who underwent chest drain as first procedure, we applied the same statistical procedure described above to estimate the independent effect of chest tube size (≤ 14 Fr and > 14 Fr) on the three outcomes.

We compared the probability of subsequent intervention according to the type of first procedure using a multivariable logistic regression. First, we grouped together the less invasive (thoracentesis + chest drain) and the more invasive (MT and upfront surgery) procedures, and then directly compared MT to upfront surgery.

A level of probability of 0.05 was used to assess the statistical significance, and the statistical analyses were performed using R version 4.3.1, and the library "quantreg" for the quantile regression.

Results
The study cohort included a total of 509 patients. More than two thirds were males (75.4%), the median age was 63 years (IQR 49–76), and most of them were never smokers (61.6%). Main demographic and clinical features of study population are summarised in Table 1, while additional features are reported in Supplementary Material S2-S3. More than half of patients had at least one comorbidity (57.0%), with diabetes mellitus type 2, cardiac failure, and active cancer being the most prevalent (12.6%, 12.2% and 9.2% respectively). The median duration of pre-admission symptoms was 7 days (IQR 5.0–10.0), and around half of patients had received antibiotics before hospitalization (51.3%). One hundred and twenty-three patients (24.2%, 95%CI 21.1–28.4) had a positive pleural fluid culture, with Streptococci ssp. being the most frequent (36%), followed by Enterobacteriaceae ssp. (21.6%) and Anaerobes (13.4%) (Supplementary Materials S4). Pleural infection was driven by community-acquired pneumonia (CAP) in 388 cases (76.0%), by hospital-acquired pneumonia (HAP) in 36 (7.1%), whilst a concomitant lung abscess was found in 31 patients (6.1%). No difference was found on microbiology positivity proportion between patients receiving antibiotic therapy prior to the hospitalisation or not (55.6% vs. 51.2%, respectively; $p = 0.492$). Pleural effusion was mostly unilateral with moderate or large size, and characterized by a purulent appearance in more than half of patients; anechoic fluid, pleural septations and loculations were the most prevalent features at TUS. Pleural fluid PH measurement was available in 18% of study cohort only ($n = 94$), with a median value of 7.0 (IQR 6.9–7.2).

Data on first-line management are summarized in Table 2. Chest drain placement overall resulted as the most used first-line approach ($n = 220$; 43.4%, 95% CI 36.1–47.9), followed by MT ($n = 122$; 24.0%, 95%CI 20.3–27.9), surgery at onset ($n = 68$; 13.4%, 95% CI 10.5–16.6), and thoracentesis ($n = 58$; 11.4%, 95%CI 8.8–14.5). Intrapleural therapy was performed in 220 patients (43.2%) and the most used fibrinolytic agent in those patients was urokinase (74.5%). About timing of intervention, 275 patients (54%) underwent first-line approach within the first 48 h (23% < 24 h; 31% 24–48 h).

MT and thoracentesis were more frequently performed within the first 24 h (44.2% and 50.0%, respectively) compared to chest drain insertion and upfront surgery (29.4% and 22.1%, respectively) (chi^2 p value = 0.003) (Supplementary Material S6).

An additional non-surgical procedure was needed in a minority of patients (17.7%), and it was most commonly chest tube placement (43.4%). Patients receiving first-line approach with chest drain insertion and thoracentesis were more likely ($p < 0.0001$) to require subsequent additional procedures (31.0% and 26.2%, respectively) compared to MT and upfront surgery (7.4% and 7.3%, respectively). (Supplementary Material S5). No significant difference was found in terms of need for additional non-surgical treatment when comparing MT and

Table 1 Main demographic and clinical characteristics of the study population

Age, median (IQR)	**63.0 (49.0,76.0)**
Male sex, n (%)	384 (75.4%)
Smoking status, n (%)	
Never smoker	305/495 (61.6%)
Current/former smoker	190/495 (38.4%)
Pre-admission antibiotics use, n (%)	
No	233/494 (47.2%)
Yes	261/494 (52.8%)
Pre-admission steroid use, n (%)	
No	360/433 (83.1%)
Yes	73/433 (16.9%)
Pneumonia source, n (%)	
CAP	388/455 (85.3%)
HAP	36/455 (7.9%)
Lung abscess	31/455 (6.8%)
RAPID Score, median (IQR)	2.0 (1.0,3.0)
At least one comorbidity, n (%)	290 (57.0%)
Comorbidities, n (%)	
Previous pneumonia (6mo before)	81/509 (15.9%)
Diabetes mellitus	64/509 (12.6%)
Heart failure	62/509 (12.2%)
Current active cancer	47/509 (9.2%)
Autoimmune-Connective tissue Diseases	28/509 (5.5%)
Chronic kidney disease	26/509 (5.1%)
Neurological disorders	25/509 (4.9%)
Immunodeficiency	23/509 (4.5%)
Other	73/509 (14.2%)
Duration of pre-admission symptoms (days), median (IQR)	7.0 (5.0,10.0)
Symptoms at admission, n (%)	
Dyspnoea	232/509 (45.6%)
Cough	178/509 (35.0%)
Chest pain	291/509 (57.2%)
Weight loss	19/509 (3.7%)
Weakness	62/509 (12.2%)
Fever	310/509 (60.9%)
Night sweat	5/509 (1.0%)
Haemoptysis	15/509 (2.9%)
Others	19/509 (3.7%)
Laterality, n (%)	
Left	225/507 (44.4%)
Right	257/507 (50.7%)
Bilateral	25/507 (4.9%)
Pleural fluid size on thoracic ultrasound, n (%)	
small (< 1 rib space)	52/457 (11.3%)
moderate (2–3 rib spaces)	252/457 (55.1%)
large (= > 4 rib spaces)	153/457 (33.5%)
Findings on thoracic ultrasound, n (%)	
Pleural thickening	52/457 (10.2%)
Pleural nodules	75/457 (14.7%)
Hyperechogenic fluid	6/457 (1.2%)
Anechoic fluid	110/457 (21.6%)
Pleural septations	132/457 (25.9%)
Pleural loculations	110/457 (21.6%)
Pleural fluid appearance, n (%)	

Table 1 (continued)

Age, median (IQR)	**63.0 (49.0,76.0)**
Serous	100/496 (20.2%)
Serous-bloody	94/496 (19.0%)
Bloody	12/496 (2.4%)
Milky (chylous-like)	2/496 (0.4%)
Purulent	288/496 (58.1%)
Microbiology positivity, n (%)	
No	373/496 (75.2%)
Yes	123/496 (24.8%)
Pleural fluid - pH, median (IQR)	7.0 (6.9,7.2)
≤ 7.2, n (%)	74/93 (79.6%)
> 7.2, n (%)	19/93 (20.4%)

Table 2 First-line management of patients with pleural infection

Type of 1 st procedure, *n* (%)	
Medical thoracoscopy	122/469 (26.0%)
Thoracentesis	58/469 (12.4%)
Chest drain	221/469 (47.1%)
Upfront surgery	68/469 (14.5%)
Chest tube size (Fr), n (%)	
≤ 14	74/221 (33.5%)
> 14	134/221 (66.5%)
Duration of tube stay (days), median (IQR)	7.0 (3.0,11.0)
Medical thoracoscopy	4.0 (3.0,7.0)
Chest drain	8.0 (5.0,12.0)
Upfront surgery	5.0 (3.0,10.0)
Medical thoracoscopy + IET	4.0 (3.0,7.0)
Chest drain + IET	10.0 (6.0,12.0)
Upfront surgery + IET	*Upfront surgery + IET*
Intrapleural therapy, n (%) *	
No	196/402 (48.7%)
Yes	206/402 (51.3%)
Fibrinolytic agent, n (%)	
Urokinase	164/220 (74.5%)
saline solution	3/220 (1.4%)
Urokinase + saline solution	53/220 (24.1%)
Time to 1 st procedure, n (%)	
< 24 h	158/430 (36.8%)
24–48 h	117/430 (27.2%)
> 48 h	155/430 (36.0%)

IET Intrapleural enzyme therapy

* This result is comprehensive of all types of first-line procedure (chest drain + medical thoracoscopy + upfront surgery)

upfront surgery (OR 2.3, 95%CI 0.7–7.8, $p = 0.163$) (data not shown). The type of first procedure was found to be independent of the RAPID score classes ($p = 0.098$). This result was confirmed also in the multivariable analysis comparing chest drain and thoracentesis to MT, after adjusting for age, RAPID score and number of comorbidities (OR 7.3, 95% CI 3.3–16.3, $p < 0.001$; OR 7.5, 95%CI 2.9–18.7, $p < 0.001$).

Subsequent surgery referral

Overall, a subsequent surgery referral was required in 135 patients (26.5%), the type of approach was VATS in 104 patients (77.0%), and the median time from admission to surgery was 9 days (IQR 5.0–15.0). Thoracentesis and chest drain significantly increased the probability of subsequent surgery referral compared to MT both in the unadjusted and in the multivariable fully adjusted analysis (OR 6.0; 95%CI 1.8–23.6; $p = 0.004$; OR 7.8 95%CI 2.6–22.5, $p < 0.001$) (Fig. 1; Table 3); in addition, for each additional comorbidity and for each additional year of age, the probability of subsequent surgery referral reduced by 29% ($p = 0.032$) and 2% ($p = 0.038$), respectively).

In the subgroup of patients treated with chest drain insertion as first procedure ($n = 221$; 43.2% of cases), a large-bore drain placement (> 14 F) had 3-times more probability of subsequent surgery referral (OR 2.9; 95% CI 1.2–6.9, $p = 0.017$) compared to patients with small-bore drain (≤ 14 F), after adjusting for RAPID score, number of comorbidities and age (Table 4).

Furthermore, patients with loculations or septations identified on baseline TUS were more likely to require subsequent surgical treatment (adjusted OR 3.1; 95% CI 1.5–6.3, $p < 0.001$) (Supplementary Material S7).

Length of stay

Overall, the median hospital LOS was 15 days (IQR: 10–24) and MT was significantly associated with a shorter median LOS compared to ches t drain ($p < 0.001$) and upfront surgery ($p = 0.002$) (Fig. 1), and this was confirmed also in the quantile linear regression. In fact, compared to MT, chest drain insertion and upfront surgery were associated with longer median hospital stay of 4.9 days (95% CI 1.5–8.4) and 5.2 days (95% CI 1.0–9.5.0.5), respectively (Table 5). Whichever pleural intervention deferred after the first 48 h was associated with a longer median hospital LOS (Regression Coefficient Estimate 5.0; 95%CI 1.5–8.6) compared to those performed within 24 h.

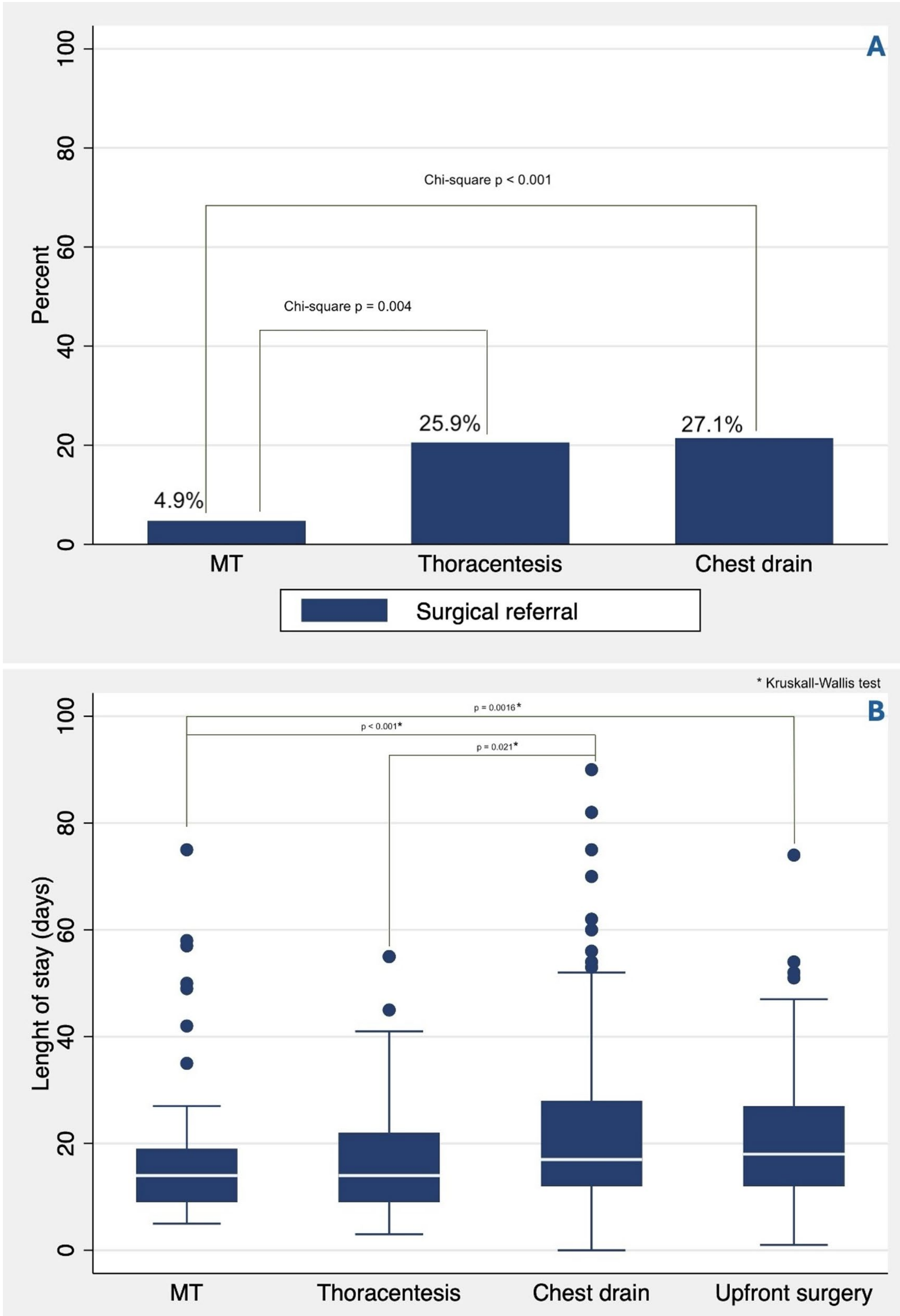

Fig. 1 Proportion of subsequent surgical referral (**A**) and median length of hospital stay in days (**B**) according to type of first procedure

Table 3 Odds of undergoing subsequent surgical referral according to type and time of 1 st procedure, adjusted for RAPID score, number of comorbidities and age. Results of multiple logistic regression model

	uOR (95% CI)	aOR (95% CI)	*p*-value
Type of 1 st procedure			
Medical thoracoscopy (r.c.)	1	1	
Thoracentesis	6.68 (2.43–18.35)	**6.03 (1.76–20.63)**	**0.01**
Chest drain	7.19 (3.00–17.20.00.20)	**7.80 (2.63–22.50)**	**< 0.001**
Time to 1 st procedure			
< 24 h (r. c.)	1	1	
24–48 h	1.04 (0.59–1.84)	1.04 (0.51–1.91)	0.88
> 48 h	4.45 (0.27–74.21)	0.91 (0.51–1.65)	0.77
RAPID score	0.62 (0.69–0.98)	0.94 (0.77–1.15)	0.55
Number of comorbidities	0.76 (0.57–1.01)	**0.71 (0.53–0.97)**	**0.03**
Age (years)	**0.98 (0.97–0.99)**	**0.98 (0.96–1.00)**	**0.04**

rc reference category, *OR* Odds Ratio, *a* adjusted, *u* unadjusted, *95%CI* 95% Confidence interval, significant values are reported in bold.

Table 4 Odds of undergoing subsequent surgical referral according to chest tube size, adjusted for RAPID score, number of comorbidities and age in patients treated with chest drain as first procedure. Results of multiple logistic regression model

	uOR (95% CI)	aOR (95% CI)	*p*-value
Chest tube size			
≤ 14 Fr (r. c.)	1		
> 14 Fr	**0.40 (0.29–0.73)**	**2.90 (1.21–6.92)**	**0.02**
RAPID score	0.62 (0.69–0.98)	1.01 (0.78–1.31)	0.92
Number of comorbidities	0.76 (0.57–1.01)	**0.55 (0.35–0.87)**	**0.01**
Age (years)	**0.98 (0.97–0.99)**	0.98 (0.96–1.01)	0.14

rc reference category, *OR* Odds Ratio, *a* adjusted, *u* unadjusted, *95%CI* 95% Confidence interval, significant values are reported in bold.

Table 5 Length of stay (days) conditioned on type of 1 st procedure, and time to 1 st procedure, adjusted for RAPID score, number of comorbidities and age. Results of multiple quantile regression model

	Regression Coefficient Estimate (unadjusted)	Regression Coefficient Estimate (adjusted)
	(95% CI)	(95% CI)
(Intercept)		**9.44 (3.41–15.46)**
Type of 1 st procedure		
Medical thoracoscopy (r.c.)		
Thoracentesis	1.81 (0.49–5.50)	2.50 (−2.16-7.16)
Chest drain	1.27 (0.49–5.51)	**4.94 (1.51–8.37)**
Upfront surgery	1.70 (0.65–7.35)	**5.20 (0.97–9.45)**
Time to 1 st procedure		
< 24 h (r.c.)	1.53 (−1.00-5.00)	
24–48 h	1.41 (1.23–6.77)	1.46 (−2.22-5.14)
> 48 h	8.84 (−19.37-15.37)	**5.04 (1.45–8.62)**
RAPID score	0.38 (−0.42-1.09)	0.70 (−0.44-1.84)
Number of comorbidities	0.57 (−0.13-2.13)	0.40 (−1.23-2.04)
Age (years)	0.03 (−0.02-0.09)	*0.02 (−0.12-0.08)

rc reference category *95%CI* 95% Confidence interval, *LL* lower level *UL* upper level, significant values are reported in bold.

Conversely, the presence of loculations/septation at the baseline US assessment did not show any impact on LOS in our fully adjusted model (Regression Coefficient Estimate 2.4; 95%CI −0.5-5.4) (Supplementary Material S7).

In the subgroup of patients treated with chest drain insertion as first procedure, the chest drain tube size was not associated with LOS (data not shown).

90-day mortality

Life status data were available for 366 out of 509 (72%) patients included in the study due to loss to follow-up. Overall, 19 out of 366 patients died within 90 days of admission (5.2%). Type, time of first procedure, and baseline TUS findings did not significantly affect the 90-day mortality (Table 6, Supplementary Material S6). For each additional unit in the RAPID score, and in the year of age, the probability of death increased respectively of 68% (95%CI 1.0–2.7.0.7, $p = 0.037$) and of 11% (95%CI 1.0–1.2.0.2, $p = 0.006$), respectively (Table 6).

In the subgroup of patients treated with chest drain insertion as first procedure, the chest drain tube size was not associated with 90-day mortality (data not shown).

Recruiting centre

We observed significant differences in the management of pleural infection across the participating centres (Supplementary Material S8). There were significant differences in terms of type and timing of first procedure and proportion of surgical referral ($p < 0.001$ in all cases). We did not detect a significant difference in terms of 90-day mortality across different centres (overall p value = 0.389).

Table 6 90-day mortality conditioned on type of 1 st procedure, and time to 1 st procedure, adjusted by RAPID score, number of comorbidities and age. Results of multiple logistic regression model

	uOR (95%CI)	aOR (95%CI)	*p*-value
Type of 1 st procedure			
Medical thoracoscopy (r. c.)	1	1	
Thoracentesis	0.25 (0.03–2.40)	0.53 (0.01–14.56)	0.71
Chest drain	0.98 (0.31–3.12)	1.63 (0.17–15.52)	0.67
Surgery at onset	0.29 (0.03–2.64)	2.03 (0.08–50.54)	0.67
Time to 1 st procedure			
< 24 h (r. c.)	1	1	
24–48 h	1.69 (0.46–6.19)	2.49 (0.29–20.96)	0.40
> 48 h	1.75 (0.51–5.97)	5.41 (0.69–42.34)	0.11
RAPID score	**2.13 (1.46–3.10)**	**1.68 (1.04–2.74)**	**0.04**
Number of comorbidities	2.04 (1.38–3.03)	1.55 (0.91–2.63)	0.10
Age (years)	**1.11 (1.06–1.17)**	**1.11 (1.03–1.20)**	**0.01**

rc reference category, *OR* Odds Ratio, *a* adjusted, *u* unadjusted *95%CI* 95% Confidence Interval, significant values are reported in bold.

Discussion

Our large-scale multicentre study focused on management and outcomes of pleural infection reveals different approaches among centres and suggests a potential crucial role of MT in this clinical scenario, as it was significantly associated to a reduced probability of subsequent surgical referral compared to thoracentesis and chest tube placement. Moreover, patients undergoing MT as first procedure experienced a shorter LOS compared to those treated with chest tube insertion or upfront surgery, though the low number in the latter subgroup is likely to influence the reliability of comparison. Similarly, a longer time to first intervention was associated with a longer LOS. On the other hand, type and timing of first procedure did not significantly impact 90-day mortality, although this study was not designed and powered to primarily investigate this outcome. Moreover, our data confirmed that age and RAPID score accurately predicted mortality.[10,15] TUS findings at admission also played a significant role on clinical evolution and management, as patients with features suggestive of complicated effusion, such as loculations or septations, were more likely to require a surgical intervention and a longer hospital stay. Finally, the placement of a large-bore drain was associated to a 3-fold higher probability of subsequently undergoing surgery, surgery referral, after adjusting for RAPID score, number of comorbidities and age. However, in daily practice, clinicians might tend to place large-bore drains in patients with a more severe clinical scenario not captured by the adjusting variables, and, thus, with an independent baseline higher risk of requiring surgery or other further interventions.

The crucial role of first procedure choice in determining the need for additional interventions has been well established. *Wozniak* et al. [18] analysed the risk of additional procedures and death depending on the first approach and they found that chest tube insertion was associated with a higher risk for further rescue procedures compared to VATS and thoracotomy. Furthermore, *Nandeesh* et al. [19] found that VATS was better than the conventional chest tube insertion in terms of hospital stay, mean duration of the chest tube in situ, mean cost of the treatment, complications and failure rate.

To our knowledge, no studies investigating the impact of early MT on the probability of surgical referral have been published, so far. Nevertheless, the potential of MT in pleural infection has also been demonstrated by *Mondoni* et al. [11], who performed a systematic review and metanalysis aiming at assessing the efficacy of MT in patients with pleural infection. They found a pooled treatment success rate of thoracoscopy of 85% (95% CI 80.0–90.0%; I2: 61.8%) when used as first-line intervention or after failure of chest tube, with a pooled complication rate was 9.0% (95% CI 6.0–14.0%; I2: 58.8%). Furthermore, *Fujita* et al. [20] retrospectively assessed the effectiveness of MT carried out by chest physicians under local anaesthesia in a single centre between 2018 and 2023. They found a treatment success in more than 94% of cases, with 6.7% of serious adverse events and no deaths.

Our data show the potential efficacy of MT in pleural infection, reducing the probability of surgical referral, even though clear explanations for the reduction in surgical referral cannot be established. However, a difficult access to theatre could be one of the main reasons, as thoracic surgery units are not widespread in Italy and MT can be promptly carried out by pulmonologists in the same health care setting.

Intuitively, the later the first intervention, the worse the outcome [21]. Concerning this, our study confirmed that assumption, except for 90-days mortality, which seemed not to be influenced by time of intervention, although the high percentage of missing values in this context may have impacted the results.

Of note, the proportion of patients with positive pleural fluid culture was surprisingly low (24.2%) compared to previous data from literature (40–60%) [22], and no significant differences were found between patients who received pre-admission antibiotics and those who did not. Potential explanations include a not widespread use of blood culture bottles in Italy, that has been reported to increase microbiology yield [23], and the lack of a standardized collection procedure. Furthermore, due to the retrospective nature of our study, we were not able to identify potential pitfalls related to collection, transport or management of the sample that might have been caused false-negative results.

Although reliability of our data on 90-days mortality could be influenced by the not negligible number of missing values, the proportion registered in study cohort was relatively low (5.2%). The latest ERS/ATS statement on the management of pleural infection in adults reported mortality rates ranging from 4.4 to 17.6% [1]. However, the accounted studies were few and out to date, while updated estimates are not yet available and data at national level have never been published, making difficult a proper comparison. In addition, we can speculate that the fact that most of centres included in our study have a longstanding expertise in pleural diseases management might have led to a more favourable survival rate.

Finally, the very limited proportion of pleural fluid pH assessment in our cohort (14%) deserves a comment. According to the most recent British Society Guideline (BTS) for pleural disease [17], *"For patients with parapneumonic effusion or suspected pleural infection, where diagnostic aspiration does not yield frank pus, an immediate pH analysis should be performed"*, as it is proposed as a key element in determining which patients can be treated with intercostal drainage (recommendation strong, by consensus), likely reflecting current expertise and daily practice of clinicians at national level. However, based on our data, it appears that Italian pleural physicians culturally rely more on TUS features rather than on pH results in their decision-making process, as documented by the large number of patients with an ultrasound evaluation at baseline (82%).

Major strengths of the present study include the large number of cases, and the representativeness of study population, as different centres across Italy with different settings and sources were involved. As a result, this study provides important information on daily clinical practice, showing different approaches in pleural infection management, as expression of different expertise and settings, as well as of the lack of robust scientific evidence in some aspects of this condition. Real-world results are particularly relevant to guide scientific community in identifying areas that might need further research by means of prospective clinical trials.

Our study also presents some weaknesses. First, the main limitation is the retrospective nature of the study, which is itself always limited by selection bias. Second, different level of expertise in each centre might have influenced the choice and timing of procedures, with a potential higher proportion of early intervention (i.e. MT within 24 h) in more experienced centres. Third, due to the retrospective nature of this study, different approaches at local level and inter-operator variability in absence of pre-defined protocols (i.e. modalities for processing PF cultures, microbiology tests used, TUS assessment), might have affected the comparability of data. Fourth, although we have included the most acknowledged confounders in our multivariable model, the possibility of unmeasured confounders cannot be excluded. Fifth, although the use of tPA + DNAse has been recommended, this treatment is not adopted and fibrinolytics use is limited in Italy. This has led us to choose chest drain only as comparator to MT, even though this is not an optimal treatment. Lastly, there was a significant proportion of missing data, mostly regarding some clinical or laboratory features (i.e., RAPID score, pH) not retrievable retrospectively.

Conclusion

In conclusion, our multi-centre observational study provides valuable insights into the management and outcomes of pleural infection with relevant implications for clinical practice.

Our study points out the importance of an early and tailored intervention in the treatment of pleural infection. Clinicians should carefully consider patient-specific characteristics, such as performance status, comorbidities, and disease stage, as well as centre-specific aspects, as expertise, settings and sources, when choosing the most appropriate treatment strategies, to optimize outcomes and minimize complications.

Finally, our results lay the foundation for further definitive exploration of MT as a primary treatment modality in pleural infection. Consequently, a national Italian multicentre randomized trial is currently being planned.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03391-7.

Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

F.M., F.G., M.B., and M.I. contributed equally to study conception and design. F.G., M.I. and R.G. performed the statistical analyses. F.G, M.I., and F.M. collected and curated the data. F.G. and F.M. drafted the main manuscript. L.C., M.S., A.D.M.B., L.Z., A.F., S.T., M.T., G.M., V.P., C.R., C.S., R.S., P.E.B., E.P., M.Ta., A.Pa., G.E.C., P.I., V.Pi., G.Pu., E.B., M.D., M.Mo., P.C., D.L., C.V., and P.I. participated in patient recruitment and data acquisition at respective centers. F.C. and R.G. supervised methodological rigor and contributed to manuscript review. All authors reviewed and approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and legal restrictions, individual-level patient data cannot be made publicly available.

Declarations

Competing interests
The authors declare no competing interests.

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