Effect of time to onset on clinical features and prognosis of post-sternotomy mediastinitis

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Abstract

Incubation time affects the clinical features and outcome of many nosocomial infections. However, its role in the setting of post-sternotomy mediastinitis (PSM) has not been specifically studied. The present study aimed to evaluate the impact of time to onset of PSM on the clinical presentation and outcomes of patients. Hospital records of 197 patients who developed PSM over a 10-year period and were treated by closed drainage using Redon catheters were reviewed retrospectively. Follow-up was complete for all included patients (median of 19 months); 98 patients developed early-onset PSM (time from initial operation to PSM <14 days) and 99 patients had late-onset PSM (≥14 days). Patients with late-onset PSM had a higher rate of internal thoracic artery harvest and mediastinal re-exploration after initial operation. Patients with early-onset PSM presented more frequently with septic shock. Microbiological findings differed between early- and late-onset PSM by a higher incidence of *Enterococcus* species in the former and of *Staphylococcus aureus* in the latter. Overall mortality reached 34% (n = 66). Rates of superinfection, treatment failure, mediastinitis-related death, mortality at 1 year and overall mortality were all significantly higher in patients with early-onset PSM. Multiple regression procedures identified early-onset PSM as a significant and independent risk factor for both 1-year (OR 2.40; 95% CI 1.12–5.11) and overall (OR 2.11; 95% 1.26–3.53) mortality. In conclusion, the results obtained in the present study support the distinction between early- and late-onset PSM with different clinical and pathophysiological features. Early-onset PSM is associated with a significantly higher morbidity and mortality compared to late-onset PSM.

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Introduction

Post-sternotomy mediastinitis (PSM) remains one of the most serious and dreaded complications of cardiac surgery. In recent series, the incidence of PSM has been reported to be in the range 1–4% and associated with increased patient morbidity, mortality and hospital costs [1]. Although numerous studies have focused on analysing risk factors for the development of PSM [2,3], only a few have focused on the prognosis and risk factors for adverse outcome of PSM. One previous attempt has been made to stratify PSM according to the time of first presentation, the presence or absence of associated risk factors, and whether previous attempts at treating the condition have failed [4]. However, the prognostic value of the individual variables used for this classification has not been validated.

Differentiating early- from late-onset PSM appears to be justifiable for several reasons. First, these two types of PSM may display different features in terms of pathophysiology, clinical presentation and microbial etiologies [5]. Second, because mediastinal tissues are still soft and pliable in the early postoperative period, debridement and surgical treatment of PSM may be facilitated [5]. Third, incubation time affects the clinical features and outcomes of many other nosocomial infections [6]. Thus, the present study aimed to evaluate, in a large series of patients, the influence of time to

onset (using a 2-week cut-off as previously suggested) [4] on the clinical features and outcomes of PSM.

Materials and Methods

Patients

Between 1 January 1996 and 28 February 2007, 7289 patients underwent a cardiac surgical procedure at Henri Mondor University Hospital, Créteil, France. Antimicrobial prophylaxis followed the guidelines of the Société Française d'Anesthésie-Réanimation. Systemic antimicrobial prophylaxis was initiated before incision and was continued for 48 h postoperatively, and used cefamandole, except when patients had risk factors for methicillin-resistant *Staphylococcus aureus* or a preoperative hospital stay exceeding 5 days (in which case vancomycin was used). PSM was defined as a deep wound infection associated with sternal osteomyelitis, with or without infection of the retrosternal space, and which needed surgical debridement. According to this definition, 212 patients developed PSM during the study period, with an overall incidence of 2.9%. Closed drainage using Redon catheters was the surgical initial therapy of choice [7]. Patients initially treated by a closed irrigation technique (n = 1), by primary soft tissue closure (n = 5) or by open drainage (n = 2) were excluded from analysis. Furthermore, patients with PSM during or after a period of mechanical circulatory support with implantable or paracorporeal devices were also excluded from the analysis (n = 5). Follow-up information was lacking for two patients. Thus, the present study comprised 197 cases of PSM. Some patients included in the present study have been reported on in a previous study [7].

Surgical management of PSM

As soon as the diagnosis of PSM was strongly suspected, intravenous antibiotic treatment was instituted. In the absence of positive cultures, empiric anti-staphylococcal therapy was administered using a combination of oxacillin or vancomycin with aminoglycosides. All patients underwent surgery on an urgent basis according to our previously described protocol (closed drainage using Redon catheters) [7]. The antibiotic regimen was adapted to the organisms recovered from the sternal wound and continued for an overall treatment duration of 4–6 weeks.

Data collection

Hospital records were reviewed retrospectively. The time to onset was defined as the interval between the initial surgical procedure and surgical debridement for mediastinitis. Early-onset and late-onset PSM were defined using a 14-day cut-off, as previously suggested by El Oakley *et al.* [4]. Obesity was defined as a body weight greater than 20% of normal weight, as estimated by the Lorentz formula. Diabetes was defined as the need for medication with an antidiabetic drug. Preoperative renal insufficiency was determined by serum creatinine levels higher than 1.5 mg/dL (130 μmol/L). Septic shock was defined according to the ACCP/SCCM Consensus Conference [8]. Life-threatening complications recorded included secondary prosthetic valve endocarditis, massive mediastinal haemorrhage caused by vascular or cardiac rupture, and occurrence of septic shock or multiple organ dysfunctions. Treatment failure was defined as the inability of the technique to resolve local infection and leading to reoperation, or as death of the patient as a consequence of mediastinal infection. Superinfection was defined as the occurrence of a subsequent episode of PSM in which a different pathogen was isolated. Complete follow-up information was available for all 197 included patients, for a median follow-up duration of 19 months.

Statistical analysis

Statistical analysis was performed using SPSS Base 10.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as the median (interquartile range) and were compared using the Mann–Whitney U-test. Categorical variables, expressed as percentages, were analysed with a chi-square test or Fisher's exact test. Survival data were analysed with standard Kaplan–Meier actuarial techniques for estimation of survival probabilities. To identify risk factors for 1-year mortality, overall mortality, mediastinitis-related death and treatment failure, univariate analysis of preoperative, procedure-related and mediastinitis-related variables was performed by comparing different subsets of patients. To evaluate independent risk factors for adverse outcome, significant univariate risk factors were examined by multiple regression procedures using backward stepwise logistic regression analysis and Cox regression. We considered that we could enter a maximum number of six variables in each model, in view of the number of events observed [9,10]. Coefficients were computed by the method of maximum likelihood. p <0.05 (two-tailed) was considered statistically significant.

Results

Patients characteristics and details of initial cardiac surgical procedure

The series comprised 151 men and 46 women, aged 66.9 ± 17.2 years.

PSM developed after a median delay of 14 ± 12 days (range 3–92 days) in the entire series, with 98 patients developing early-onset PSM (time to onset <14 days) and 99 patients having late-onset PSM (time to onset ≥14 days; Fig. 1). Table 1 shows the clinical characteristics of the two groups of patients. No significant differences were found between the two groups with respect to age, sex and preoperative cardiac status. The prevalence of the classical preoperative risk factors for PSM (including obesity, chronic bronchopulmonary airway disease and use of immunosuppressive drugs) was not significantly different between the two groups. Details of the initial surgical procedure are reported in Table 2. The duration of cardiopulmonary bypass was similar in patients with early-onset PSM and those with late-onset PSM: 146 ± 99 min vs. 145 ± 88 min (p 0.29).

Aortic cross-clamp time was also comparable between the two groups: 95 ± 68 min for early-onset PSM vs. 97 ± 71 min for late-onset PSM (p 0.78). There was a more frequent use of internal mammary arterial grafts in patients with late-onset PSM compared to those with early-onset PSM: 71 (72%) vs. 54 (55%) (p 0.02). Mediastinal re-exploration after the initial cardiac procedure was marginally more frequent in patients with late-onset PSM compared to those with early-onset PSM: 17 (17%) vs. 7 (7%) (p 0.05). Autologous blood transfusion was administered during the immediate postoperative course to 55 patients (56%) in the early-onset PSM group and to 52 patients (53%) in the late-onset PSM group (p 0.67).

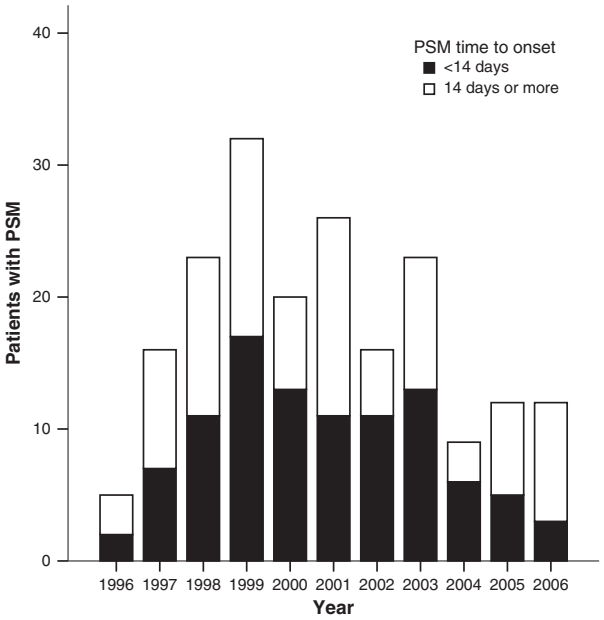

FIG. 1. Patients with early-onset and late-onset post-sternotomy mediastinitis according to year of enrollment. PSM, post sternotomy medistinitis; Year 2007 has been omitted because the enrollment of patients ended in February 2007 (there were three PSM recorded within the first 2 months of 2007, all with early-onset delay).

PSM

The time to onset of PSM was 9 ± 4 days in the early-onset group and 20 ± 12 days in the late-onset group. Pathogens isolated from sternal wounds during debridement are reported in Table 3. There was a significantly higher prevalence of *Enterococcus* spp. in patients with early-onset PSM, whereas methicillin-sensitive *S. aureus* was more frequent in late-onset PSM. The rate of concomitant bloodstream infection was similar in the two groups: 53 (54%) for early-onset PSM vs. 53 (54%) for late-onset PSM (p >0.99). Patients with early-onset PSM exhibited an almost two-fold higher prevalence of predrainage septic shock compared to others: 24 (24%) vs. 13 (13%) (p 0.04). Sixteen patients (8%) developed mediastinitis after 30 days, including two presenting with predrainage septic shock; in these patients, infection was caused by methicillin-susceptible *S. aureus* (*n* = 6), methicillin-resistant *S. aureus* (*n* = 5), coagulase-negative *Staphylococcus* (*n* = 1), *Serratia* sp (*n* = 1), *mycoplasma* (*n* = 1) and polymicrobial infection (*n* = 2).

Morbidity and mortality of PSM

All patients were treated with surgical debridement and closed drainage using Redon catheters. Closed drainage duration was similar between groups: 16 ± 8 days for early-onset PSM vs. 15 ± 6 days for late-onset PSM (p 0.35). More patients in the early-onset PSM group needed postoperative surveillance in an intensive care unit (ICU) compared to those with late-onset PSM: 71 (72%) vs. 50 (51%) (p <0.01). There was an apparent trend, although this was not statistically significant toward a higher rate of ventilatory support for more than 24 h in patients with early-onset PSM compared to the others: 35 (36%) vs. 23 (23%) (p 0.078). The duration of ICU stay (in those requiring ICU after drainage) did not differ between groups: 9 ± 14 days for early-onset PSM vs. 7 ± 14 days for late-onset PSM (p 0.24). Life-threatening complications occurred marginally more frequently in patients with early-onset PSM compared to the others: 21 (21%) vs. 11 (11%) (p 0.05). Life-threatening complications included multiple organ failure in 25 (12.6%), major mediastinal bleeding in three (1.5%) and secondary prosthetic valve endocarditis in two (1.2%) patients, as well as stroke in one (0.5%) and mesenteric ischaemia in one (0.5%) patient. The overall mortality rate was 34% (66 patients); it was 43% and 24%, respectively, in early- and late-onset PSM (Table 4). Actuarial overall survival estimates were 82 ± 3% at 1 month, 72 ± 3% at 1 year, 70 ± 3% at 2 years, 64 ± 4% at 3 years and 63 ± 4% at 4 years (Fig. 2). Twenty-nine deaths

TABLE 1. Preoperative characteristics of patients with early-onset and late-onset mediastinitis

	All patients (*n* = 197)	Early-onset mediastinitis (*n* = 98)	Late-onset mediastinitis (*n* = 99)	p
Age, years	66.9 ± 17.2	66.4 ± 17.2	67.3 ± 18.3	0.57
Male sex, *n* (%)	151 (77)	81 (83)	70 (71)	0.06
New York Heart Association functional class	2.0 ± 1.0	2.0 ± 1.0	2.0 ± 1.0	0.22
Renal insufficiency, *n* (%)	23 (12)	13 (13)	10 (10)	0.51
Chronic obstructive pulmonary disease, *n* (%)	20 (10)	11 (11)	9 (9)	0.65
Immunosuppressive drugs, *n* (%)	15 (8)	4 (4)	11 (11)	0.10
Diabetes, *n* (%)	69 (35)	29 (30)	40 (40)	0.14
Obesity, *n* (%)	47 (24)	20 (20)	27 (27)	0.32

TABLE 2. Details of initial surgical procedures in patients with early-onset and late-onset mediastinitis

	All patients (*n* = 197)	Early-onset mediastinitis (*n* = 98)	Late-onset mediastinitis (*n* = 99)	p
Emergency surgery, *n* (%)	54 (27)	32 (33)	22 (22)	0.11
Redo surgery, *n* (%)	29 (15)	18 (18)	11 (11)	0.17
Procedure, *n* (%)				
CABG	105 (53)	51 (52)	54 (54)	0.54
Valve procedure	33 (17)	18 (18)	15 (15)	
Combined CABG plus valve procedure	38 (19)	17 (17)	21 (21)	
Aortic root replacement ± valve procedure	11 (6)	7 (7)	4 (4)	
Orthotopic heart transplantation	8 (4)	3 (3)	5 (5)	
Other	2 (1)	2 (2)	0 (0)	

CABG, coronary artery bypass grafting.

TABLE 3. Causative organisms of early-onset and late-onset mediastinitis

	All patients (*n* = 197)	Early-onset mediastinitis (*n* = 98)	Late-onset mediastinitis (*n* = 99)	p
Gram-positive cocci				
Staphylococcus aureus				
Methicillin susceptible	78 (40)	27 (28)	51 (52)	<0.01
Methicillin resistant	23 (12)	12 (12)	11 (11)	0.83
Coagulase-negative *Staphylococcus*	38 (19)	23 (23)	15 (15)	0.15
Enterococcus spp.[a]	17 (9)	15 (15)	2 (2)	<0.01
Streptococcus spp.	4 (2)	3 (3)	1 (1)	0.37
Gram-negative bacilli				
KES	27 (14)	15 (15)	12 (12)	
Escherichia coli	22 (11)	14 (14)	8 (8)	0.18
Proteus spp.	9 (5)	5 (5)	4 (4)	0.75
Pseudomonas spp.	6 (3)	1 (1)	5 (5)	0.21
Citrobacter	5 (3)	3 (3)	2 (2)	0.68
Morganella	4 (2)	2 (2)	2 (2)	>0.99
Mycoplasma	2 (1)	1 (1)	1 (1)	>0.99
Negative culture	5 (3)	2 (2)	3 (3)	>0.99
Fungi	1 (1)	0 (0)	1 (1)	>0.99
Polymicrobial	38 (19)	20 (20)	18 (18)	0.72

[a]All *Enterococcus* spp. were susceptible to vancomycin.
KES, *Klebsiella*, *Enterobacter* and *Serratia*; data are *n* (%).

where directly attributable to mediastinitis (23 cases of sepsis and six cases of major mediastinal haemorrhage), whereas 37 others were not (six cases of unrelated sepsis, nine cases of cardiac deaths, four cases of stroke, eight cases of other origin and ten deaths of unknown origin). The rates of superinfection, treatment failure, mediastinitis-related death, mortality at 1 year and overall mortality were all significantly higher in patients with early-onset PSM compared to those with late-onset PSM (Fig. 2, Table 4).

Factors associated with adverse outcome

Univariate analysis revealed that older age, male sex, preoperative renal insufficiency, combined coronary artery bypass grafting (CABG) plus valve procedures, early-onset PSM and predrainage septic shock were significant risk factors for both 1-year and overall mortality (Table 5). Logistic regression analysis identified older age, renal failure, early-onset PSM, combined CABG plus valve procedures, and predrainage septic shock as independent risk factors for 1-year

TABLE 4. Outcome of early-onset and late-onset mediastinitis

	All patients (*n* = 197)	Early-onset mediastinitis (*n* = 98)	Late-onset mediastinitis (*n* = 99)	p
Reintervention for recurrent mediastinitis, *n* (%)	21 (11)	12 (12)	9 (9)	0.50
Superinfection, *n* (%)	8 (4)	7 (7)	1 (1)	0.04
Treatment failure, *n* (%)	41 (21)	28 (29)	13 (13)	<0.01
Mediastinitis-related death, *n* (%)	29 (15)	22 (22)	7 (7)	<0.01
Mortality at 1 year, *n* (%)	54 (27)	35 (36)	19 (19)	0.01
Overall mortality[a], *n* (%)	66 (34)	42 (43)	24 (24)	<0.01

[a]Mortality recorded during the median 19 months of follow-up.

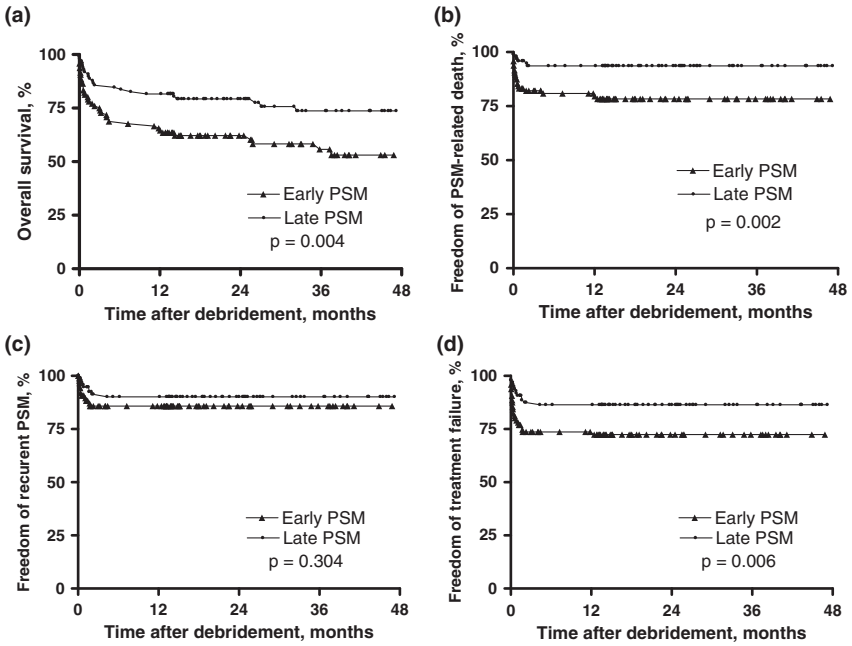

FIG. 2. Actuarial estimates for overall survival (a), freedom of mediastinitis-related death (b), freedom of recurrent mediastinitis (c), and freedom of treatment failure (d) in patients with early-onset and late-onset mediastinitis. PSM, post-sternotomy mediastinitis.

TABLE 5. Risk factors for adverse outcome after mediastinitis (*n* = 197)

Variable	Univariate analysis p value	Multiple regression procedure[a], OR (95% CI)
One-year mortality (events = 54)		
Age (per 1 year)	<0.001	1.06 (1.02–1.10)
Male sex	0.03	–
Renal failure	<0.01	3.99 (1.35–11.79)
Time to onset <14 days	<0.01	2.40 (1.12–5.11)
Combined CABG plus valve procedure	<0.01	2.59 (1.03–6.46)
Predrainage septic shock	<0.001	3.59 (1.51–8.50)
Overall mortality during follow-up (events = 66)		
Age (per 1 year)	<0.001	1.05 (1.02–1.07)
Male sex	0.03	–
Renal failure	<0.01	3.00 (1.60–5.62)
Time to onset <14 days	<0.01	2.11 (1.26–3.53)
Combined CABG plus valve procedure	<0.01	–
Predrainage septic shock	<0.001	2.43 (1.42–4.18)

[a]Logistic regression for 1-year mortality and Cox regression for overall mortality.
CABG, coronary artery bypass grafting.
The Hosmer and Lemeshow goodness of fit test showed a good calibration of the logistic regression model: χ^2 (d.f. = 8) = 3.9, p 0.89.

mortality (Table 5). Cox regression analysis identified older age, renal failure, early-onset PSM and predrainage septic shock as independent risk factors for overall mortality (Table 5). Cox analysis restricted to mediastinitis-related deaths confirmed that early-onset PSM was significantly associated with mortality (OR 3.4; 95% 1.44–8.05), together with age and predrainage septic shock. Early-onset PSM was also associated with treatment failure by Cox analysis (OR 2.26; 95% 1.15–4.44), along with age, predrainage septic shock and methicillin-resistant *S. aureus* (MRSA) infection.

Discussion

The main finding of the present study was that PSM exhibited different clinical features and outcomes, depending on time to onset. Early-onset PSM (i.e. occurring less than 14 days after initial cardiac operation) was associated with

significantly higher rates of septic shock, treatment failure, mediastinitis-related death, 1-year and overall mortality compared to late-onset PSM.

The occurrence of surgical wound infection and the duration of its incubation period are determined by a complex interplay between: (i) patient-related factors; (ii) wound-related factors such as extent of tissue trauma, dead space and haematoma; and (iii) microbial factors such as microbial load and virulence. Wound contamination occurs most frequently during primary operation by direct inoculation or airborne contamination [11]. Direct contamination of the wound by the patient's endogenous flora at the time of surgery is considered to be the most common mechanism [12]. Indeed, current methods of preoperative skin preparation and cutaneous antisepsis can reduce but not eliminate skin-associated bacteria in surgical patients. Accordingly, Kühme *et al.* [13] showed that 89% of patients yielded bacteria from the subcutaneous sternal tissue and 98% of patients showed bacterial growth on the surrounding skin at the end of the operation. Alternatively, wound contamination can occur at a later time point during the postoperative course. Direct inoculation can occur during re-operation because of bleeding or for pericardial drainage. This is consistent with the significantly higher incidence of reoperations that we observed in the late-onset PSM group. Furthermore, haematogenous seeding of a surgical wound late after cardiac surgery has been reported [11]. Although its importance relative to intra-operative inoculation remains unknown, the former mechanism can be assumed to be marginal. Thus, it is highly probable that most infections observed in the present study were the consequence of intra-operative wound contamination, and the delay between initial cardiac operation and reoperation for PSM can be considered to be representative of the incubation period. However, knowledge of the precise starting day of mediastinitis-related symptoms would have improved our analysis.

The impact of time to onset on the outcome of PSM remains controversial. In a previous study, we reported that early-onset PSM was a risk factor for mediastinitis-related death [7]. By contrast, Trouillet *et al.* [14] found that incubation time had no influence on ICU mortality in patients treated for PSM. However, the latter study was confined to patients requiring ICU admission and the follow-up restricted to ICU mortality. De Feo *et al.* [15] reported that an increased 'interval between initial symptoms and debridement' was a predictor of unfavourable outcome following mediastinitis; however, this interval can not be considered as the time to onset of mediastinitis and more likely reflects a delay in surgical treatment initiation after mediastinitis onset. We hereby demonstrate the prognostic impact of time to onset in a large series of patients with long-term follow-up. The other factors associated with 1-year mortality by multiple regression procedures were increased age, renal failure, combined CABG plus valve procedures, and predrainage septic shock. Some of these results are in accordance with those of Karra *et al.* [16] who reported that increased age and renal failure were associated with 1-year mortality after mediastinitis, along with other variables related to disease severity before debridement (ICU stay), type of organism involved (MRSA) or treatment modalities (lack of flap closure, increased time to flap closure after sternal debridement, and ineffective antibiotic treatment against the infecting organism within 7 days of debridement). In their study [16], the mean delay between initial operation and diagnosis of mediastinitis was not significantly shorter in patients who had died at 1 year compared to 1-year survivors (21 days vs. 26 days; p 0.34), although this result is difficult to compare with ours, considering that the variables assessed were different and treatment options were very dissimilar between studies.

In the present study, we found no significant differences in patient-related risk factors for PSM between patients who developed early-onset or late-onset infections. However, several studies have shown that major surgery and more specifically cardiac surgery with cardiopulmonary bypass induces a systemic inflammatory response syndrome (SIRS) along with its anti-inflammatory counterpart [17].

Reduced postoperative human leucocyte antigen-DR expression has been shown to be predictive of subsequent infective complications [18]. Many of these alterations persist at least during the first postoperative week. Thus, it might be speculated that PSM can occur earlier and is more frequently associated with adverse outcomes in those patients who demonstrate the most pronounced SIRS and have the most profound immunoparalysis. This is consistent with our finding that early-onset PSM presented significantly more frequently with septic shock than late-onset PSM.

Conversely, PSM can be expected to have longer incubation times in patients in whom immunological defenses are less altered. In these patients, the development of PSM may be more strongly influenced by local wound factors. Accordingly, in addition to the higher reoperation rate mentioned above, internal thoracic arteries were used more frequently in patients developing late-onset PSM. Internal thoracic artery harvesting results in partial sternal devascularization, which may compromise tissue healing and local defenses.

Microbiological findings in early-onset and late-onset PSM differed substantially, but are unlikely to explain the different outcomes observed between early and late mediastinal infection in the present study. There was a higher incidence of *Enterococcus* species in early-onset PSM, whereas a higher incidence of *S. aureus* (essentially methicillin-susceptible) was

recorded in late-onset cases. This pattern is most certainly related to the selective pressure exerted by current antimicrobial prophylaxis, which is mainly targeted to staphylococcal species and is usually based on a cephalosporin. Prophylactic antimicrobials are given to assist natural host defences to eradicate bacteria that have contaminated the wound. In the case of staphylococcal contamination, this strategy likely allows avoiding early postoperative staphylococcal infection in most patients and probably retards its clinical expression in others. Conversely, pathogens that are not covered by prophylaxis will tend to develop more rapidly and declare themselves earlier. Thus, *Enterococcus* species, which are resistant to all cephalosporins and are becoming increasingly resistant to vancomycin [19], were isolated significantly more frequently in early-onset PSM. However, it is not clear that the use of cephalosorins was solely responsible for this fact. No *Enterococcus* outbreak was identified during the study period and all *Enterococcus* isolates recovered from our patients were susceptible to vancomycin.

Overall, the high incidence of staphylococcal infections suggests that our patients might benefit from routine preoperative nasal administration of mupirocin to eliminate staphylococcal colonization, as recommended by the 2007 guidelines of the Society of Thoracic Surgeons [20]. Furthermore, 38% of PSM were caused by Gram-negative bacteria, suggesting incomplete coverage by the antimicrobial prophylaxis regimen used. Additional measures, such as the use of an aminoglycoside either systemically [20] or locally [21,22] to act as a specific anti-Gram-negative agent when vancomycin is indicated as a primary prophylactic agent, might be beneficial. The results obtained in the present study suggest that a high degree of suspicion should be maintained in the early postoperative period in patients at risk of PSM.

In this regard, a liberal use of sternal puncture for early diagnosis could be suggested [23]. Furthermore, given the poorer outcome of early-onset PSM, an early aggressive debridement could prove useful in this setting [15]. Recently, improved clinical results using vacuum-assisted closure versus conventional techniques, including closed drainage techniques, have been reported [1]. However, these results warrant confirmation in randomized trials and it would be speculative to draw any specific management recommendations for early-onset PSM based on the present study.

In conclusion, the results obtained in the present study support the stratification of PSM into two categories of early- and late-onset cases. Early-onset PSM incurs a significantly higher morbidity and mortality compared to late-onset PSM.

Transparency Declaration

The authors declare no conflict of interest of any nature.

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