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Subsegmental Pulmonary Embolism and Anticoagulant Therapy: The Impact of Clinical Context

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ABSTRACT

Background: Anticoagulation for subsegmental pulmonary embolism (SSPE) is controversial.

Aim: We aimed to assess the impact of clinical context on anticoagulation and outcomes of SSPE.

Methods: We electronically searched computed tomographic pulmonary angiogram reports to identify SSPE. We extracted demographic, risk factor, investigations and outcome data from the electronic medical record. We stratified patients according to anticoagulation/no-anticoagulation.

Results: From January 1st 2017 to December 31st 2019, we identified 166 patients with SSPE in 5,827 pulmonary angiogram reports. Of these, 123 (74%) received anticoagulation. Compared with non-anticoagulated patients such patients had a different clinical context: higher rates of previous venous thromboembolism (11% vs 0%, $p = 0.019$), more recent surgery (26% vs 9%, $p = 0.015$), more elevated serum D-dimer (22% vs 5%, $p = 0.004$), more lung parenchymal abnormalities (76% vs 61%, $p = 0.037$) and were almost twice as likely to require inpatient care (76% vs 42%, $p < 0.001$). Such patients also had twice the all-cause mortality at one year (32% vs 16%).

Conclusions: SSPE is diagnosed in almost 3% of pulmonary angiograms and is associated with high mortality, regardless of anticoagulation, due to coexistent disease processes rather than SSPE. Anticoagulation appears dominant but markedly affected by the clinical context of risk factors, alternative indications, and illness severity. Thus, the controversy is partly artificial because anticoagulation after SSPE is clinically contextual with SSPE as only one of several factors.

INTRODUCTION

Pulmonary embolism (PE) is a common, potentially fatal condition [1-6]. In addition to resuscitation in severe cases, the mainstay of PE management is anticoagulation [7]. Management considerations, however, require characterisation and risk stratification of PE. The importance of anatomic location and extent remains controversial, especially for subsegmental pulmonary embolism (SSPE) with concern about a false positive finding in the setting of a single subsegmental PE. Additionally, there is limited clinical data describing current clinical anticoagulation practice, factors influencing the decision to prescribe anticoagulant medications, and the long-term outcome of such patients. This is exemplified by the qualification of currently available evidence on anticoagulation of SSPE as weak by the American and European society guidelines [8, 9]. Such data is needed to inform clinical decision-making in this setting and to understand how best to design future trials in patients with SSPE. However, no such information has yet been presented in the literature.

Accordingly, in a university-affiliated hospital, over a three-year period, we studied all patients diagnosed with SSPE by computed tomographic pulmonary angiogram (CTPA) to study the clinical context of treatment decisions (anticoagulation versus conservative management), and associated long-term outcomes. We hypothesised that anticoagulant therapy would be strongly influenced by clinical context, that pulmonary embolism would not be the primary admission diagnosis in most cases and that high long-term mortality would be related to underlying medical conditions rather than recurrent major PE.

MATERIAL AND METHODS

Patient and data collection

The Austin Health Human Research Ethics Committee approved this retrospective cohort study with waiver of informed consent (reference Audit/20/Austin/87).

All patients undergoing CTPA examination between January 1st 2017 and December 31st 2019 at a single Australian tertiary care centre were identified using the Radiology Information System (RIS). CTPA reports that diagnosed SSPE were identified, using a bespoke in-house database. Natural language search for "subsegmental," "sub segmental" and "sub-segmental" was performed to narrow the number of included CTPA reports. Manual review of these reports to identify all instances of confirmed SSPE was performed, with reports excluded if the term was preceded by a negative (absent, no, not, negative for), combined SSPE and non-SSPE, or where the reporting radiologist specified uncertainty regarding possible SSPE, leaving only patients with one or more confirmed SSPE. Parenchymal changes and other radiological findings documented in the report were recorded. Reports using diminutive wording to qualify the diagnosis of SSPE, such as "small", "tiny" or "of uncertain clinical significance" were recorded.

As clinical decisions were made based upon the result of these finalised radiology reports, additional radiological image review in the setting of this study was not performed. All radiology reports were reported or reviewed by a senior radiologist, as part of normal clinical practice.

Patients with SSPE were stratified according to the presence or absence of therapeutic anticoagulation for >24 hours. Primary outcomes were all-cause mortality at 90 days and 12 months following SSPE diagnosis, as recorded in the electronic medical record (EMR).

Reported cause of inpatient death was recorded where available. Secondary outcomes included unplanned hospital readmissions and haemorrhagic complications. Haemorrhagic complications were defined as all instances of new unexplained decrease in haemoglobin below the local laboratory reference range lower limit or genitourinary, gastrointestinal, intracranial and spinal/epidural bleeding, recorded in the EMR.

Covariate data collected from the RIS included results of further investigations such as lower limb venous Doppler ultrasound, ventilation/perfusion (V/Q) scan and repeat CTPA. Additional covariate data collected is specified in Supplementary eTable 1.

Data analysis

Results were reported as numbers, percentages and means (standard deviation) for normally distributed data or medians (interquartile range) for skewed data. Fisher's exact test was used for univariate analyses to compare patient characteristics according to whether individuals were therapeutically anticoagulated or managed conservatively. Odds ratios (OR) with 95% confidence intervals (CI) were presented for variables with statistically significant differences where possible. Univariate (anticoagulation vs conservative) and multivariate (anticoagulation, age, hospital admission and recent surgery) Cox Proportional-Hazards models were used to assess for possible predictors of mortality at 12-months. P-value <0.05 was deemed statistically significant. All analyses were performed using Microsoft Excel™ and RStudio Statistical Software, version 1.4.1106 (RStudio: Integrated Development for R, PBC, Boston, Massachusetts, USA).

RESULTS

During the 36-month study period, 5,827 CTPA studies were performed, including 2,558 studies containing the keyword search criteria. The search yielded 167 reports with a diagnosis

of SSPE in 166 patients (Supplementary eFigure 1). One patient had two positive CTPA studies, including a repeat confirmatory study seven days after initial diagnosis.

Of the 166 patients with SSPE, 123 (74%) received therapeutic anticoagulation for > 24 hours and 43 (26%) did not. Of those managed with anticoagulation, six were previously anticoagulated for another indication (five for atrial fibrillation (AF) and one for previous VTE) and 17 had a previous history of AF but were commenced on anticoagulation following the diagnosis of SSPE.

Those managed conservatively (without therapeutic anticoagulation) included 35 patients who were never anticoagulated and eight patients who received a single initial dose of anticoagulant (short-lived anticoagulation). Causes for cessation of short-lived anticoagulation therapy included: revised primary diagnosis, pre-existing transfusion dependence (high risk gastrointestinal (GI) angiodysplasia), haematuria as a presenting complaint, changed goals of care to palliation, high falls risk (three patients), and other acute conditions thought more contributory to symptoms and thought more likely to explain the patient's presentation.

Radiology reports qualifying the presence of SSPE (e.g., "small", "tiny", "probable", "non-occlusive", "of doubtful significance") was not significantly different (P = 0.272) between the anticoagulated (37%) and conservatively managed group (44%).

Clinical characteristics

Both groups had similar age and sex distribution and baseline comorbidity burden (Table 1). Predisposing factors (defined by the Wells' criteria), however, differed. In particular, previous VTE and surgery in the prior six months were more common in the anticoagulated group. This was also true for elevated serum D-dimer (Table 1).

Patients in the conservative group (40%) were more likely to have no recorded risk factor as per the Wells' criteria or other indication for anticoagulation compared to the anticoagulated group (24%) (P = 0.050). Overall, 57 patients had very low predicted risk of PE according to Wells' criteria with no other indications for anticoagulation. The demographics, clinical characteristics and outcomes of these patients are highlighted in Supplementary eTable 2. Of low-risk patients, 30 (64%) received anticoagulation. The major significant difference between anticoagulated low risk patients (67%) and non-anticoagulated low risk patients (24%) was the percentage who were managed as inpatients (P = 0.005).

Additional radiology findings or investigations

Additional lung parenchymal abnormalities were observed in 72% of all CTPA reports, as defined in Supplementary eTable 1. Such findings were present in a significantly greater percentage of patients who were subsequently anticoagulated (Figure 1). Additional investigations are highlighted in Table 2. Overall, 35% and 23% of patients in the anticoagulation and conservative groups, respectively, had ultrasound studies after the diagnosis of SSPE, of which 20% were positive for deep vein thrombosis in each group. Troponin I measurement was numerically more common in anticoagulated patients (P = 0.057). Those who were anticoagulated had serum D-dimer measured more frequently, and were more likely to have arterial blood gas analysis.

Anticoagulant medications used

Therapeutic anticoagulation with heparin-based agents was used for initial management in approximately 78% of treated patients. Factor Xa direct inhibitors (apixaban, rivaroxaban) were administered as initial therapeutic anticoagulation to 16% of patients. Overall, 40% of patients were discharged on heparin-based therapy and 51% on oral anti-Xa agents (Supplementary eFigure 2).

Clinical outcomes

Table 3 summarises the clinical course for each study group. Although a similar proportion of patients had their CTPAs performed in the Emergency Department (ED), 76% of those in the anticoagulation group went on to receive inpatient hospital-based management compared to 42% in the conservative group (OR = 4.31 (2.07–8.96), P < 0.001). PE was coded as the primary discharge diagnosis in the EMR in 27% vs 18%, P = 0.220.

Overall, 18 patients underwent reassessment with V/Q (16 from the anticoagulation group and two from the conservative group) and one patient was reassessed for residual/recurrent PE with CTPA (anticoagulation group), between one and six months following the initial diagnosis of SSPE. All follow-up V/Q studies were negative and the single CTPA result was indeterminate.

Overall all-cause mortality rates at 90 days and 12 months after CTPA with an SSPE were 16% (27/166) and 22% (37/166), respectively. There was no statistically significant difference in mortality rates between the anticoagulation and conservatively managed groups at 90 days (21% vs 16%, P = 0.416). However, one year mortality was twice as high in anticoagulated patients (32% vs 16%, P = 0.150) following CTPA (univariate and multivariate Cox regression model results are presented in Supplementary eTables 3 and 4). Recurrent major PE or major bleeding as well as the suspected cause of death was not recorded in the EMR for any patient. Bleeding complication rates within six months of CTPA were not significantly different between the two groups (Figures 2a and 2b), however, 26% of patients in the anticoagulation group required unplanned readmission to hospital within six months compared to 9% in the conservative group (OR = 3.43 (1.14–10.35), P = 0.011).

DISCUSSION

Key findings

We conducted a computer-assisted identification of all patients with CTPA reports over three-years in a university-affiliated hospital to study the impact of clinical context on the treatment and long-term outcome of SSPE. Approximately 3% of CTPA reports diagnosed SSPE. About three in four such patients received therapeutic anticoagulation. However, anticoagulated patients had higher levels of serum D-dimer, rates of recent surgery and more prior recorded instances of VTE, known risk factors for acute PE. They were more severely ill as indicated by a greater likelihood of additional lung parenchymal abnormalities, greater likelihood of receiving inpatient hospital management, and a three-fold greater hospital readmission rate unrelated to anticoagulation. Moreover, in more than 80% of cases SSPE was not the primary admission diagnosis. All-cause mortality at 12 months was high overall, but twice as high in these higher risk patients.

Relationship to previous studies

Improved CT resolution and imaging techniques have improved the diagnosis of PE [10]. Thus, SSPE diagnosis increased from 4.7% (single-detector CTPA) to 9.4% (multi-detector CT), with numbers further compounded by the ubiquity of CT scanners in emergency departments [10, 11]. However, several controversies surround SSPE: low interobserver diagnostic reliability [12], lack of understanding of the natural history in non-cancer patients [13], and uncertainty regarding the risk/benefit ratio of anticoagulation [14].

A 2013 comparative analysis of two prospective studies of patients with SSPE, all managed with anticoagulation, reported an increased risk of new VTE after 3-month follow-up [15]. In contrast, a 2018 meta-analysis found patients with untreated SSPE did not have a higher rate

of recurrent VTE or a greater mortality rate after a similar follow-up period [16]. However, evidence supports the view that many patients with SSPE are in a prothrombotic state, e.g. D-dimer levels in patients with SSPE are significantly higher compared to those without SSPE , and similar to those with more proximal emboli [17].

Previous studies focused on specific higher risk populations (e.g. patients with known risk factors only [18], ICU patients [19], ED and inpatients only [20]). In studies assessing all patients with suspected PE, reported SSPE rates range from 0.4% to 3.6% across a total of 220 to 10,453 radiological studies (i.e. V/Q, CTPA and/or pulmonary angiography) [21-25]. Our findings of 2.9% SSPEs in 5,827 studies are aligned with previous reports. To our knowledge, the largest previously described population of patients with SSPE was reported in 2022 [26], with 292 described cases in an undisclosed number of patients with clinically suspected PE. However, this study excluded patients with active cancer, a finding we observed in one third of our cohort, making outcome comparisons based on therapy impossible. Similarly, the above study excluded patients requiring supplemental oxygen, inpatient management and a history of VTE, while not providing details of non-SSPE findings on CTPA. Thus, our study is one of the largest to date and the only one to provide what we consider fundamental to the interpretation of both therapy and outcome: granular details of the clinical context.

In addition, rates of anticoagulation for SSPE vary from 52% to 100% [10,16,24,27]. Our study fits within this range, with an anticoagulation rate of 74%.

Two previous retrospective studies described further Doppler ultrasound investigation for 27% to 97% of patients with SSPE, with positivity rates of 9% and 19% [24,27]. Our findings broadly align with these studies, with ultrasound rates of 32% and positivity rates of 21%. Interestingly, further investigation with Doppler ultrasound occurred in only 20% of conservatively managed patients. Reported rates of Doppler ultrasound at diagnosis vary

greatly among existing retrospective studies (0% to 68%) [15,18-20,22-24]. In two recent prospective studies, deep venous thrombosis (DVT) was observed in 10 of 48 patients (21%) [27] and 28 of 292 patients (10%) [26].

Studies of bleeding events reported rates of 2-6% in treated patients with SSPE [13,15,24,26,28,29]. Our study is aligned with previous findings, with a 7% bleeding rate. However, two patients (5%) in the non-anticoagulated group also had a bleeding episode.

Finally, 90-day all-cause mortality was higher in our study at 16%, compared to 1.5-10% in previous reports [15,16,26,28]. In this regard, a recent abstract from a study seeking to describe differences between patients with multiple SSPE versus isolated SSPE in 225 patients reported a 100-person year death rate which was approximately twice that seen in our cohort in a population with a 58% rate of active cancer [29]. No other study has reported on all-cause mortality at 12 months.

Strengths and limitations

To our knowledge, this study of patients with SSPE is one of the largest to date, the only one to assess and describe several risk factors, to provide the most detailed information on clinical course, consideration of treatment decisions, and the longest follow-up period. As such, it provides novel information to guide clinicians' understanding of current practice and making informed decisions related to treatment and prognosis. Crucially it demonstrates that SSPE is not the primary admission diagnosis in most patients; that the decision to anticoagulate appears instead affected by consideration of the clinical context, and that mortality at 12 months is high because of the associated pathology of which SSPE is just one manifestation.

We acknowledge several other study limitations, including the single centre and retrospective nature. The latter resulted in unequal groups of anticoagulated and non-anticoagulated patients,

which limits our ability to perform multivariable logistic regression analysis. However, our findings illustrate the heterogeneity of these patients and the fact that SSPE occurs within specific additional clinical contexts that greatly influence both the decision for or against anticoagulation as well as the final outcome. Symptomatic PE was the primary diagnosis in less than a quarter of patients, while approximately two thirds of patients had a non-VTE related lung parenchymal abnormality on CTPA. As such, a limitation of our study is that we were unable to apportion symptoms to one or two small SSPE in the presence of such confounders. Finally, we could not report on the specific length of anticoagulation in this cohort, nor on the cause of death for 25 patients (19 in the anticoagulation group and 7 in the conservative group) due to the varied follow-up settings and lack of electronic medication recording for outpatient or general practice management and the absence of post-mortem examination to detect or exclude pulmonary embolism.

CONCLUSIONS

Our findings imply that anticoagulation-related decisions are markedly contextual and influenced by previous VTE, recent surgery, elevated D-dimer levels and the presence or absence of contraindications. Moreover, our observations suggest that patients treated with anticoagulants are more severely ill, have more additional lung parenchymal abnormalities, and much greater likelihood of inpatient management. Finally, our findings suggest that one in five patients with SSPE can be expected to die within one of year of diagnosis with mortality at one year reflecting the underlying conditions and being twice as high in those receiving anticoagulation. These observations suggest that future trials of SSPE management should include a usual care arm as the control group and that, in the absence of major recurrent PE or bleeding, the administration or withholding of anticoagulation is unlikely to affect mortality.

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Figure 1: Bar chart comparing non-PE findings included in each CTPA report for each group. The grey bars describe findings seen in the anticoagulation group while the black bars describe those in the conservatively managed group.

Figures 2a and 2b: Tree charts describing the short and long-term clinical outcomes for the patients in each group. 2a = anticoagulation group; 2b = conservatively managed (i.e., not anticoagulated) group. Cause of death was only known in those who died during an inpatient admission, as documented on the death certificate. LOS = length of stay; ICU = Intensive care unit; GI = gastrointestinal.

Table 1: Demographic and clinical characteristics of study patients

	Anticoagulation (n = 123, 74%)	Conservative (n = 43, 26%)[a]	Odds Ratio (95% confidence interval)	P
Female sex	57 (46%)	22 (51%)		0.356
Age in years				
Median (IQR)	69 (59-76)	65 (54-81)		
Charlson Comorbidity Index[b]				
Median (IQR)	1 (0-2)	1 (0-3)		
Previous anticoagulation[c]	6 (5%)	0 (0%)		
Non-biochemical PE risk factors as per Wells' Criteria				
Previous PE/DVT	**13 (11%)**	**0 (0%)**	**N/A**	**0.019**
Malignancy	37 (30%)	16 (37%)	0.73 (0.35, 1.50)	0.249
Surgery in the last six months	**32 (26%)**	**4 (9%)**	**3.48 (1.14, 10.35)**	**0.015**
Haemoptysis[d]	3 (2%)	4 (9%)	0.24 (0.05, 1.14)	0.075
Tachycardia[e]	31/123 (25%)	10/26 (38%)	0.54 (0.22, 1.31)	0.129
No risk factor as per Wells' or other indication for anticoagulation	30/123 (24%)	17/43 (40%)	0.49 (0.24, 1.03)	0.050
Ambulance arrival[f]	26/47 (55%)	5/9 (56%)	0.99 (0.24, 4.16)	0.644
Unit of admission	(n = 93/123)	(n = 18/43)		
Respiratory medicine	13 (14%)	3 (17%)	0.81 (0.21, 3.20)	0.503

Haematology/oncology	17 (18%)	4 (22%)	0.78 (0.23, 2.68)	0.456
Other	63 (68%)	11 (61%)	1.34 (0.47, 3.79)	0.385

Data are presented as n and n (%). P values are displayed individually.
IQR: interquartile range.

a) 8 /43 were initially anticoagulated and then ceased within 24 hours, either after inpatient review or prior to discharge (see text).
b) Available in 121/123 anticoagulated patients and 29/43 conservatively managed patients.
c) Defined as the total number of patients on therapeutic anticoagulation prior to their diagnosis of SSPE.
d) as stated in the CTPA request
e) Vitals only available for those diagnosed in ED or as inpatients; tachycardia defined as HR > 100 bpm.

Data available for the majority of those scanned in the emergency department.

Table 2: Additional relevant investigations

	Anticoagulation (74%, n = 123)	Conservative (26%, n = 43)	P
D-dimer level measured	**28 (23%)**	**2 (5%)**	**0.004**
D-dimer >500 ng/L	27 (96%)	2 (100%)	0.933
Median level (IQR)	2,160 (1,211-3,720)	1,398 (1,299-1,498)	
Troponin T			
Number of patients tested	56 (46%)	13 (30%)	0.057
Mean difference troponin[a] (SD)	43.6 +/- 179.9	4.8 +/- 14.2	
Arterial blood gases	**33 (27%)**	**4 (9%)**	**0.011**
Lower limb venous Doppler ultrasound	43 (35%)	10 (23%)	0.109
Proportion positive	9 (21%)	2 (20%)	0.673
Ventilation/perfusion (V/Q) study	4 (3%)	0 (0%)	0.298
Proportion positive	2 (50%)	N/A	
Further CTPA	0 (0%)	1 (2.3%)	0.259
Proportion positive	N/A	1 (100%)	

Data are presented as n and n (%). P values are displayed individually.
IQR: interquartile range; SD: standard deviation; CTPA: Computer Tomography Pulmonary Angiogram

a) Mean difference in troponin alludes to the trajectory of troponin for each individual patient, i.e., the difference between peak and trough troponin levels.

Table 3: Clinical course

	Anticoagulation (74%, n = 123)	**Conservative (26%, n = 43)**	**P**
CTPA performed in ED	55 (45%)	16 (37%)	0.250
Abnormal vital signs at diagnosis	45/123 (37%)	11/26 (42%)	0.369
Managed as inpatient	**93 (76%)**	**18 (42%)**	**<0.001**
Length of stay in days			
Median (IQR)	8.5 (4.7-17.1)	8.0 (5.7-14.4)	0.400
ICU stay required	5/93 (5%)	0 /18(0%)	0.406
Rapid response team (RRT) review[a]	31/93 (33%)	6/18 (33%)	0.600
PE as the primary discharge diagnosis	32/123 (27%)	6/33 (18%)	0.216

Data are presented as n and n (%). P values are displayed individually.
IQR: interquartile range

a) One or more RRT calls during inpatient admission

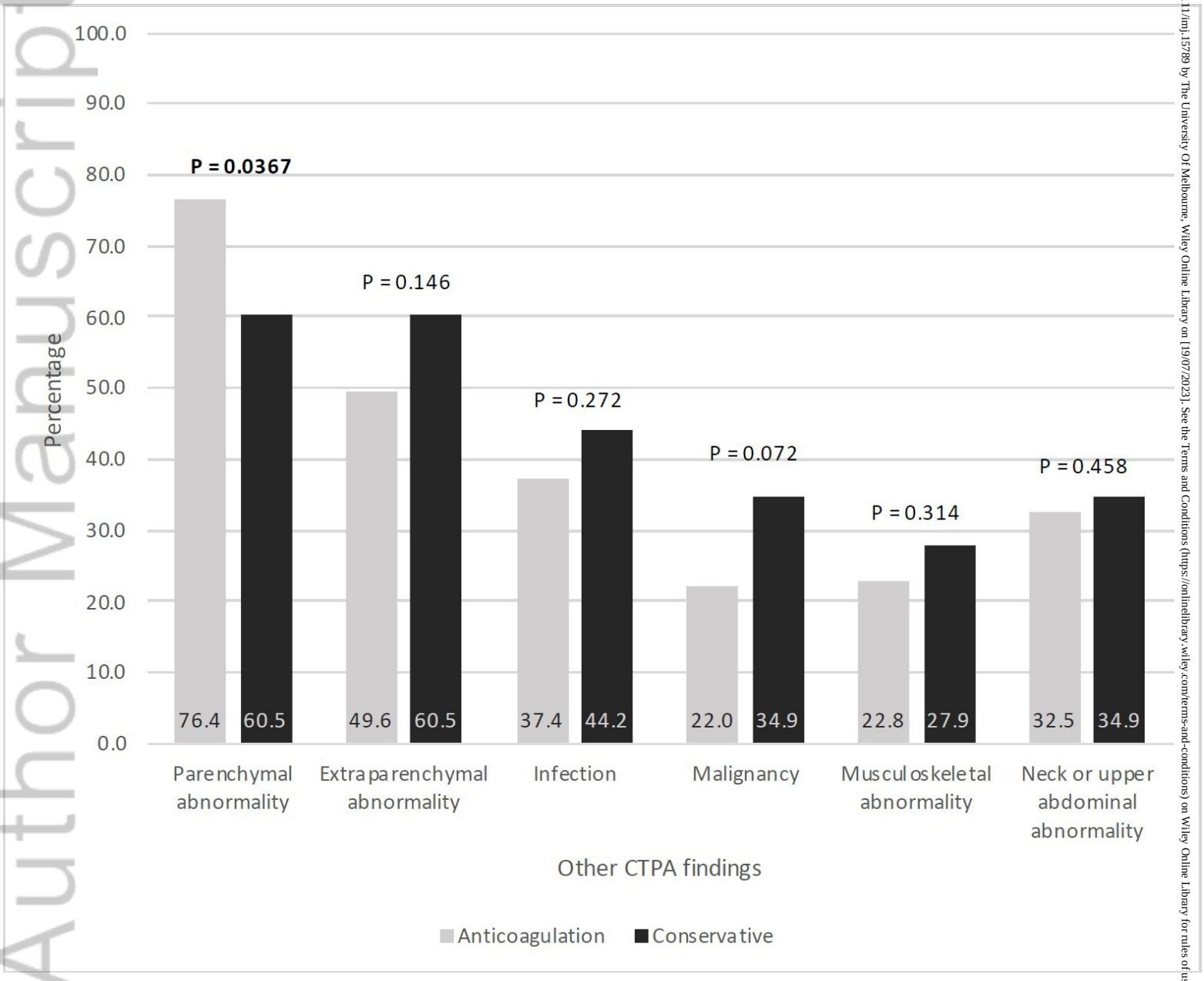

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Figure 2a: Anticoagulation group

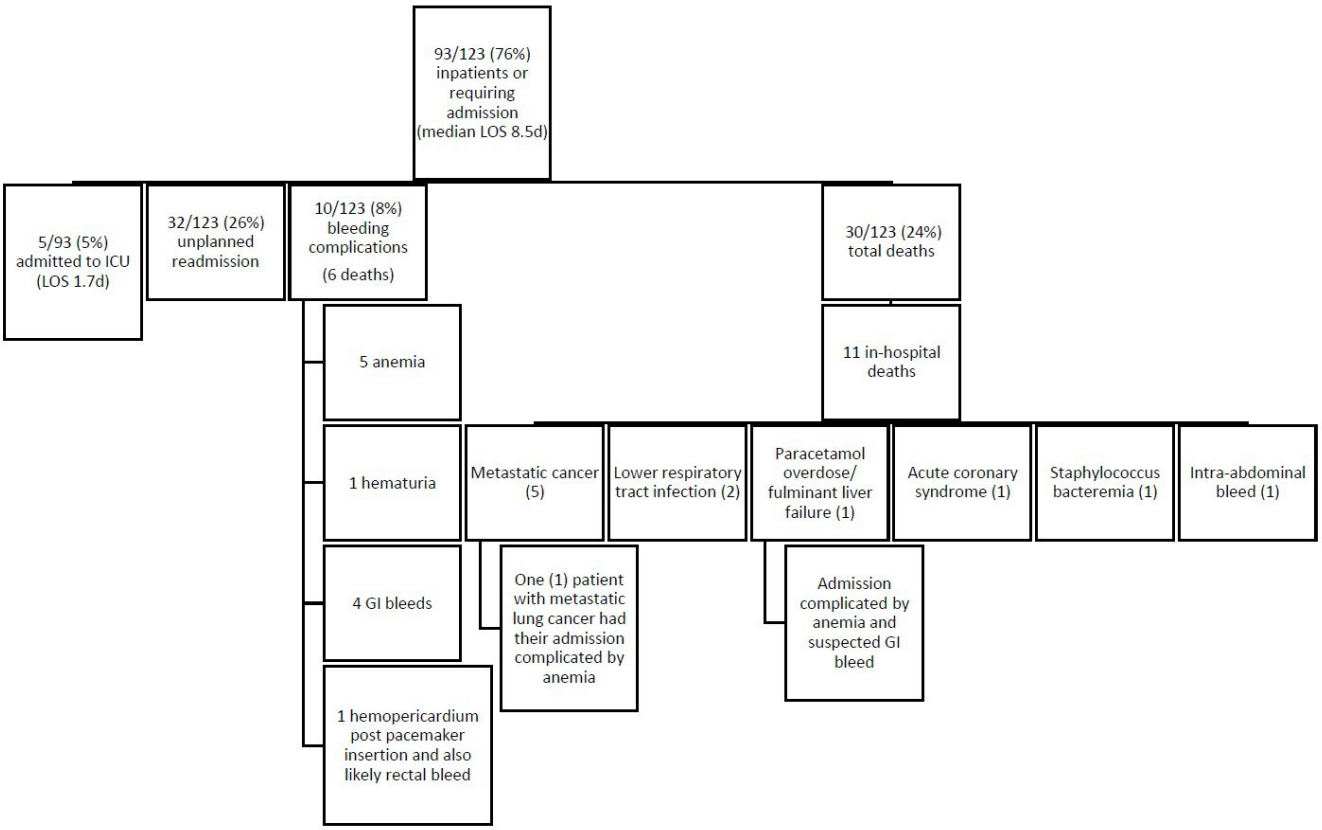

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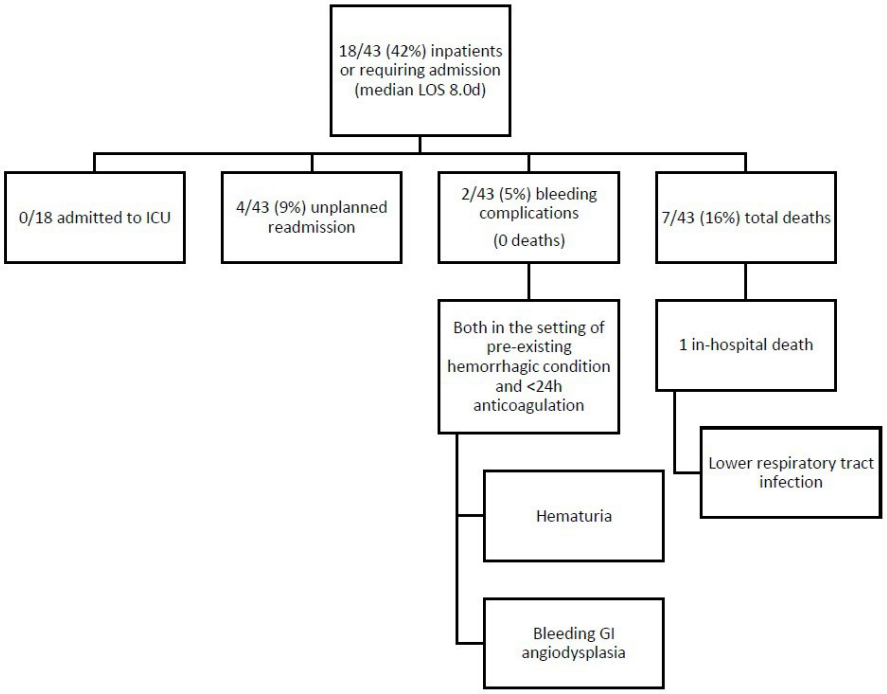
Figure 2b: No anticoagulation group



LOS, length of stay; GI, gastrointestinal; ICU, intensive care unit.

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