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REVIEW

Fat embolism: a systematic review to facilitate the development of standardised procedures in pathology

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Fat embolism (FE) is a historically recognised but still actively researched topic in forensic pathology. Several aspects remain not fully elucidated, such as its aetiopathogenesis, its causal role in death determination, the impact of interfering factors (e.g. cardiopulmonary resuscitation or other medical procedures) and both qualitative and quantitative diagnostic methodologies in clinical and forensic contexts. These issues are further underscored by the potential involvement of FE in the causal determination of non-traumatic deaths, which often raises questions of professional liability. The present study aims to provide a comprehensive and up-to-date overview of the most recent scientific evidence relevant to forensic pathology. Our systematic research has included 58 articles from 1990 to the present on the topic of FE and fat embolism syndrome (FES). From these articles, we identified 45 case reports, from which the authors' descriptions were extracted to provide information on individual cases and the operational methods of forensic pathologists. Additionally, 21 experimental studies were identified, and their key findings have been summarised narratively. It has emerged that both traumatic and non-traumatic cases are frequently reported in the forensic context, with orthopaedic and cosmetic surgery being among the highest-risk specialities. Experimental studies have re-evaluated the role of a patent foramen ovale in the pathogenesis of FE, as well as the impact of cardiopulmonary resuscitation in causing FE severe enough to result in death. Additionally, there are new findings regarding diagnostic techniques, including radiological and immunohistological methods; however, they have not yet fully bridged the reliability gap compared to an accurate autopsy–histological evaluation. The major critical points that emerged include the lack of complete and detailed information on premortem clinical conditions, the underutilisation of grading systems and the methodological heterogeneity applied, resulting in considerable variability regarding the organs studied histologically and the diagnostic techniques used. Despite the limitations associated with the analysis of case reports and the heterogeneity of included experimental studies, we believe that this study can provide a comprehensive

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Abbreviations: BM, bone marrow; CFE, cerebral fat embolism; CPR, cardiopulmonary resuscitation; FE, fat embolism; FES, fat embolism syndrome; ICC, infusion by intraosseous catheter; IPFE, isolated pulmonary fat embolism; KFE, kidney fat embolism; PBME, pulmonary bone marrow embolisms; PFE, pulmonary fat embolism; PFO, patent foramen ovale; PMCT, postmortem computed tomography; PMMR, postmortem magnetic resonance.

overview of the FE topic. It furnishes pathologists with an updated overview useful for clinical practice and guiding future research trends, as well as facilitating the development of standardised procedures.

Keywords: autopsy, fat embolism, fat embolism syndrome, findings, pathophysiology, postmortem examination

Introduction

Fat embolism (FE) is a form of parenchymal embolism caused by the entry of fat globules into the bloodstream, potentially leading to vascular occlusions. The fat emboli that enter the venous circulation primarily reach the pulmonary circulation by passing through the right sections of the heart, presenting a condition known as pulmonary fat embolism (PFE) when confined to the lungs.

When fat globules transit from the pulmonary circulation into the systemic circulation and become lodged in systemic organs, particularly the brain, kidneys, skin, eyes or myocardium, they cause a complex clinical condition characterised by multisystem involvement. Fat emboli alone can be harmless or may induce a life-threatening syndrome, known as fat embolism syndrome (FES), which is a clinical diagnosis based on specific symptoms and signs.[1] As a systemic condition, the clinical presentation encompasses multiple organ systems.[2] Therefore, the clinical presentation may include: (i) respiratory symptoms such as hypoxaemia, tachypnoea and dyspnoea, potentially progressing to acute respiratory distress syndrome (ARDS); (ii) neurological symptoms including confusion, seizures or focal neurological deficits; and (iii) dermatological symptoms such as petechial rash, which is often non-blanching and located on the upper body.

Concerning the aetiopathogenesis of FE, two not mutually exclusive theories have been historically described: the mechanical explanation by Gauss in 1924[3] and the biochemical explanation by Lehman and Moore in 1927.[4] The mechanical theory posits that fat embolisation is caused by the fracture of a long bone, which results in the laceration of intra-osseous blood vessels and the venous aspiration of disrupted fat globules from the bone marrow (BM).[5] By the same principle, during arthroplasty and intramedullary instrumentation, the increase in intramedullary pressure forces fat into the veins.[6]

Various hypotheses have been proposed to explain the systemic passage of fat emboli, including the presence of a patent foramen ovale (PFO), found in 20–25% of adults,[7] or arteriovenous shunts in the subpleural regions of the lungs, which open during increased pulmonary pressure due to FE.[8]

However, these hypotheses do not explain the systemic symptoms that can develop in individuals without a PFO or the fact that the symptomatology can be independent of the size of the circulating fat emboli.[9]

To explain these occurrences, the biochemical theory proposed by Lehman and Moore has been further explored. These authors challenged the purely mechanical explanation of FE, arguing that if free fat is present in the bloodstream, it can aggregate into particles that might plug a capillary. They supported their theory by reviewing cases showing FE in various non-traumatic conditions (e.g. metabolic disturbances such as diabetes, cardiovascular–renal syndrome, poisonings, toxaemias from acute infections and toxaemias from tissue destruction such as burns). Their pathogenetic hypothesis posited that an ultramicroscopic emulsion of fat in normal blood plasma could coarsen due to physical or chemical changes (e.g. protein decomposition products altering the surface tension of the emulsion), forming droplets large enough to cause embolism.

An extension of this theory attempted to link the signs and symptoms of FE to the inflammatory response triggered by the mobilisation and embolisation of adipose deposits following a chemical insult or trauma. In particular, there would be a release of lipase following the pulmonary embolisation of BM fat, leading to the liberation of free fatty acids (FFAs) and other lipids into the bloodstream.[10] FFAs and other lipid mediators prompt the activation of neutrophils and other immune cells, which subsequently release proinflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6. This cascade can precipitate acute respiratory distress syndrome (ARDS). As a direct result of pulmonary capillary obstruction, interstitial haemorrhage, alveolar oedema, alveolar collapse and hypoxaemic vasoconstriction ensue.[7,11] Furthermore, the release of BM-derived adipose tissue into circulation, which is highly prothrombotic, triggers platelet and fibrin

aggregation reactions, initiating a cascade of coagulation. This cascade can lead to thrombocytopaenia and, in extreme cases, disseminated intravascular coagulation.[7] The combination of the effects of these two mechanisms leads to the development of FES.

Over time, various clinical diagnostic criteria have been developed for FES, among which the most commonly used is that proposed by Gurd and Wilson, which includes major and minor features.[12] The major features include disturbances of consciousness, respiratory symptoms with radiographic changes and petechial rash. Minor features include tachycardia, pyrexia, retinal fat or petechiae, urinary fat globules or oliguria or anuria, a sudden drop in haemoglobin levels, sudden thrombocytopaenia, high erythrocyte sedimentation rate and fat globules in sputum. Other classifications include Lindeque's, which focuses on respiratory symptoms, and Schonfeld's, who developed a scoring system based on his assessment of the most important characteristics.[10]

Regardless of the classification system, respiratory distress, neurological manifestations and petechial rash represent the classic clinical triad of FES.[13] The onset of symptoms of FES typically occurs between 12 and 72 h after injury, with an average onset time of 48 h. In cases of massive FE the clinical onset is fulminant, and patients rapidly develop symptoms such as right ventricular dysfunction, cardiac failure, acute respiratory distress syndrome, cardiovascular shock and death.

Epidemiology and incidence

From an epidemiological perspective, Eriksson *et al.*[14] defined FES as the 'undiagnosed epidemic' due to autopsy findings of fat emboli in the pulmonary circulation in 82% of trauma patients and 88% of patients who received cardiopulmonary resuscitation (CPR).

However, the clinical manifestation of FES is much less common, with an incidence of 0.9% in all long bone fractures[15] and 0.17% in all fractures.[16] FE has also been reported in the paediatric population, including during the neonatal period and infancy,[17,18] with FE identified in 30% of paediatric cadavers at autopsy.[14] These numbers are extremely low in this age group when considering only FES.[16] Hypotheses regarding this discrepancy have pointed to the low percentage of adipose tissue in paediatric BM, or its biochemical composition.[14,16] The accurate estimation of the prevalence of FES is nonetheless complicated by possible non-traumatic causes of the condition.

Some of these include (i) forensic causes such as burns or hypothermia[19] and (ii) medical cases such as cosmetic surgery (e.g. liposuction/lipoinjection),[20–23] cardiopulmonary bypass surgery, complications of diabetes mellitus, decompression sickness, intra-osseous infusion of corticosteroid therapy,[24] acupuncture,[25] parenteral lipid infusion and caesarean delivery.[26]

Some studies have reported the development of FE in patients affected by sickle cell disease[27] arising from BM necrosis. Moreover, another cause could be haemorrhagic pancreatitis,[28,29] a pathology characterised by massive fat necrosis, with an increased likelihood of lipid agglutination.[30] FE has also been reported in cases of hepatogenic causes[31,32] and carbon tetrachloride poisoning with massive hepatic necrosis.[33]

Given the significant heterogeneity of causes of FE, it should be considered as a cause of death when adipose emboli are found in pulmonary and cerebral vessels during autopsy, especially if a rapid collapse has been observed clinically and no other appropriate cause of death is identifiable or ascertainable at autopsy.[13]

Especially in cases where circumstances and clinical information are incomplete, there is a real risk of underestimating FES. This is why the diagnosis of FES is often reliant on autopsy and histopathological examination. Several histological staining techniques can be utilised to detect FE. Among the most important are Oil red O staining, Sudan III, Sudan black, Sudan red G, Sudan IV and Osmium tetroxide. Additionally, there are immunohistochemical techniques using anti-CD61 and anti-fibrinogen antibodies that allow the visualisation of platelet aggregates at the edge of fat globules and an absorbed fibrinogen layer at the interface of fat globules.[34]

An anecdotal, cost-effective technique for examining FE at autopsy was described by Sigrist in 1988. This method employs a twin-edged knife,[35] a specialised tool with sharp edges on both sides, to collect tissue samples approximately 0.25 mm thick (up to 0.5 mm), which can then be directly examined under a microscope (after being placed on a slide) with or without staining. Recently, Voisard and colleagues adopted this method in a study on the incidence of FE in Iceland.[36]

Conversely, it has been proposed that technologically advanced tools are necessary for a proper qualitative and quantitative diagnostic method for FE.[37] Regarding this latter point, multiple histopathological grading systems are available to evaluate the severity of FE (Table 1).

Table 1. Grading systems of fat embolism syndrome based on evaluation of fat embolism within pulmonary vessels

Authors	Histopathological grade	Shape	Staining
Bunai *et al.*[38]	NR	Quantitative	Osmium tetroxide
Busuttil *et al.*[39]	Fat embolism index	Quantitative	Osmium tetroxide
Emson[40]	Mild	20/unit area	Oil red O
	Moderate	21–60/unit area	
	Severe	> 60/unit area	
Falzi *et al.*[41]	0	None	NR
	1	Dome	
	2	Sausage/round	
	3	Antler	
Fineschi/Turillazzi *et al.*[37]	0 (A)	No emboli	H&E, Sudan III
	1 (A)	Sporadic presence	
	2 (B)	Slight embolism	
	3 (C)	Moderate embolism	
	4 (D)	Massive embolism	
Mason[42]	0	No emboli found	Oil red O
	1	Emboli found after some searching	
	2	Emboli easily found	
	3	Emboli present in large numbers	
	4	Emboli present in potentially fatal numbers.	
Mudd *et al.*[43]	0	No emboli (× 4)	Osmium tetroxide
	1	1–10 emboli (× 4)	
	2	1–5 emboli (× 10)	
	3	1–5 emboli (× 40)	
	4	≥ 5 emboli (× 40)	
Sevitt[44]	Slight (1)	< 1 per field	NR
	Moderate (2)	1–3 per field	
	Gross (3)	> 3 per field	

H&E, haematoxylin and eosin; NR, not reported.

Aims and scope

The present study aims to provide a comprehensive and up-to-date overview of the most recent scientific evidence relevant to forensic pathology. We have endeavoured to collect and analyse both the most significant case reports and experimental studies conducted to delve into various aspects of FE. To the best of our knowledge, there is currently no systematic review in the literature that compiles all the key evidence in this field. Therefore, we have schematically outlined the characteristics of individual cases,

highlighting the operational procedures currently used by forensic pathologists in approaching FE cases. Additionally, we have descriptively reported the findings from the most recent studies, which provide insights into controversial issues (e.g. the role of CPR or the significance of FE in determining the cause of death). We believe that our work can be useful: (i) in providing updated evidence to forensic pathologists in legal contexts; (ii) as a basis for the future development of standardised procedures; and (iii) in suggesting new directions for future research, particularly in histopathological diagnosis.

Materials and methods

Our quantitative systematic review was conducted from January 2024 to April 2024 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines.[45,46]

LITERATURE SEARCH

The process of identifying eligible studies for the systematic review is outlined in Figure 1. Potential articles were identified from Scopus, Pubmed and Google Scholar.

Initially, no temporal filters were applied. For the search on Scopus, the keywords used were 'TITLE-ABS-KEY-AUTH (lipid*) AND/OR TITLE-ABS-KEY-AUTH (fat*) AND TI-TLE-ABS-KEY-AUTH (embolism*) AND TITLE-ABS-KEY-AUTH (forensic*)'. For the search on PubMed, the keywords used were '[(lipid *) AND/OR (fat*)] AND (embolism*) AND (forensic*) any field'. Emerging reviews and reference lists of the retrieved papers were also searched manually by two investigators (D.M. and M.S.). Google Scholar was inspected manually, entering the same search keywords used for searches on other databases. As a first step the results from various

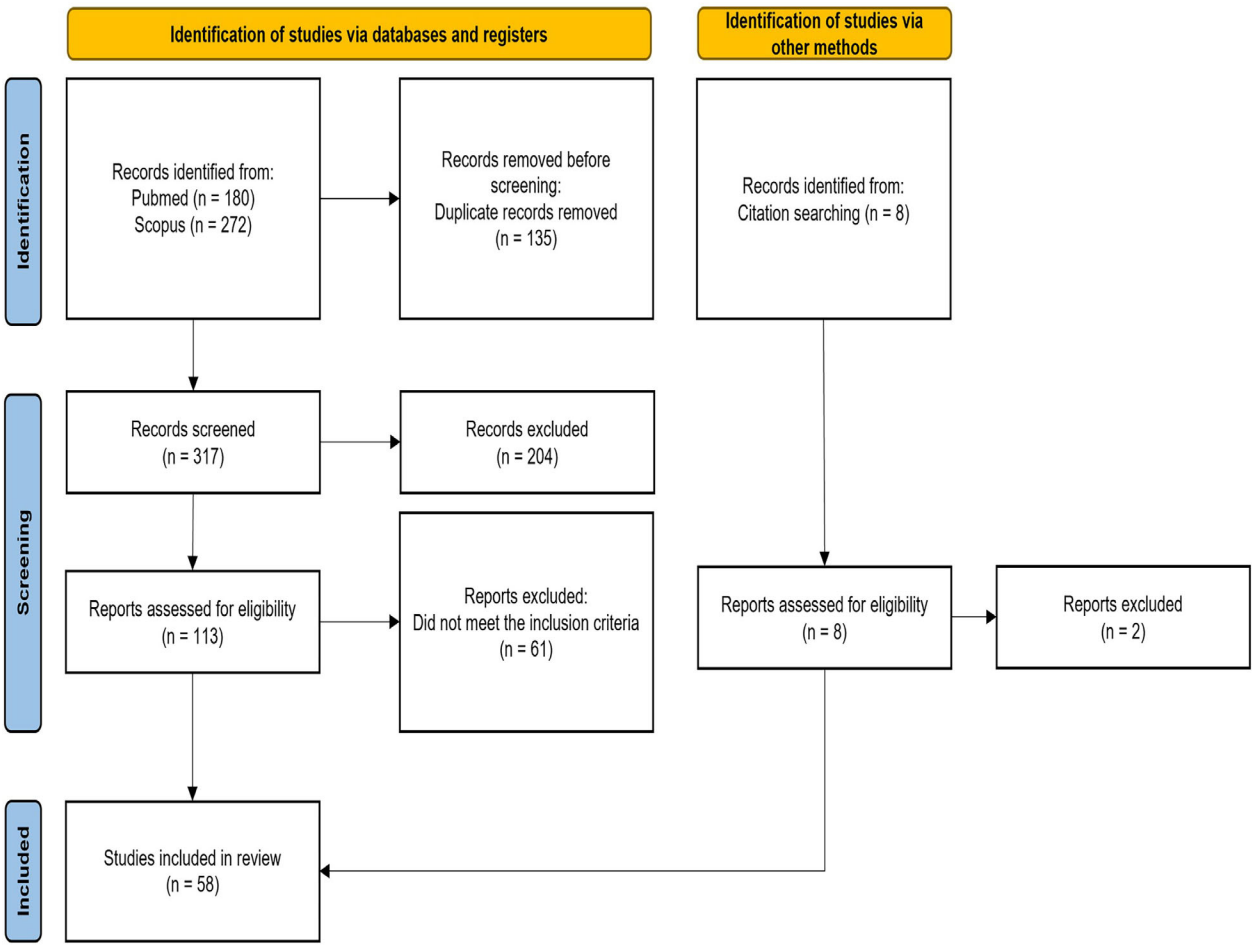

Figure 1. Our review strategy following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standards.

databases were combined, and duplicates were removed. Eligibility screening was conducted on the abstracts of papers identified through the described procedures. Papers that passed this initial screening process underwent a more comprehensive assessment for potential inclusion in our study, which involved a thorough examination of the full text. The exclusion criteria initially included non-English language and non-human studies. Subsequently, a temporal selection was also necessary due to the volume of studies found, excluding all studies before 1990. Additionally, studies not published in peer-reviewed journals were excluded. Two independent reviewers (D.M. and M.S.) evaluated the reports and extracted data; any disagreements were resolved by a third author (either E.T. or V.F.).

DATA EXTRACTION

A standardised form was utilised to extract data from the included studies involving case reports, facilitating the synthesis of evidence. Extracted information included the year of publication and the author(s); type of FE (i.e. FE, PFE, FES); case characteristics such as age, sex, underlying diseases; stress factors, the main event, the application of cardiopulmonary resuscitation (CPR), the organs investigated at the histological level and if they were interested by FE; the grading system utilised; and the cause of death as identified by the author(s). The cases were divided into two main categories: traumatic and non-traumatic. Extraction was independently conducted by two reviewers (D.M. and M.S.) in duplicate. A third reviewer (V.F.) was consulted when needed.

Results

Initially, we found 452 studies (PubMed = 180; Scopus = 272), from which 62 duplicates were automatically removed and an additional 73 were manually eliminated (n = 317). The title and abstract review allowed for the selection of 113 potentially eligible contributions. Additionally, eight potentially eligible contributions were identified through reference screening and a search on Google Scholar. After reviewing the full content of the papers, 61 studies were excluded from the main group and two papers from the additional group (for the list of the included and excluded studies see the supplementary data file published as Supporting information online attached to the electronic version of this paper).

The studies included (n = 58) were then initially divided into two categories:

1. The studies that included case reports, totalling 45 cases whose clinical and forensic characteristics could be categorised and analysed (see Supporting information, Tables S1 and S2); and
2. The studies that included research programmes on the topic. Of the 21 studies found, the majority (n = 10, 47.6%) were observational, six (28.6%) were prospective, four (19%) were reviews, one (4.8%) included both a case report and a survey, and an analysis of autopsy records.[47]

RESULTS FROM THE CASE REPORTS

The review of articles allowed us to identify 45 cases from 1990 to the present. Of these, 12 cases (26.7%) were classified as FE, 14 (31.1%) as FES and 17 (37.8%) as PFE; 17 cases (37.8%) were associated with antecedent trauma, while 28 cases (62.2%) were non-traumatic. Of these latter, eight (28.6%) were forms of an embolism following non-cosmetic surgical procedures; five (17.9%) followed cosmetic procedures such as liposuction and lipoinjection; 13 (46.5%) were related to various other causes; in two cases, it was not possible to clearly ascertain the non-traumatic cause.[24]

CPR procedures were reported in 28 cases (62.2%), while in 10 cases (22.2%) no resuscitation manoeuvres were performed (in seven cases, data were missing).

Of the 28 CPR-positive cases, nine were in the traumatic group and 19 in the non-traumatic group; of the 10 CPR-negative cases, seven were in the traumatic group and three in the non-traumatic group (χ^2 = 6.44, d.f. = 2; P = 0.040).

In the majority of studies (n = 40, 88.9%), including those diagnosing FES, clinical criteria supporting a diagnosis according to known systems in the literature (Gurd and Wilson, Schonfeld *et al.*, Lindeque *et al.*) were not reported. The criteria of Gurd and Wilson were explicitly applied in only three studies (6.7%), while clinical data useful for diagnosis according to a diagnostic system were present in only 23 cases (51.1%). Among these, a complete diagnosis of FES could be made *post-hoc* in 13 cases (28.9%) and partial (one major criterion and less than four minor criteria) in eight (17.8%), while no major criteria were met in two cases (4.4%).

We analysed a particularly critical clinical criterion, sudden thrombocytopaenia, finding that data

were reported in only 13 cases (28.9%), with a decrease present in six cases (46.2%), of which three were traumatic and three were non-traumatic ($\chi^2 = 1.67$, d.f. = 2; $P = 0.435$).

The explicit application of one of the grading systems for quantitative analysis was present in 20 cases (44.4%). Falzi's criteria were applied in 13 cases, Sevitt's in three, Mason's in two, Mudd *et al.*'s in one and Turillazzi/Fineschi's in one, while other known criteria in the literature (e.g. Emson, Bunai, Busuttil) were not applied.

Regarding staining systems, only haematoxylin and eosin (H&E) was used in 14 cases (31.1%), while in a higher percentage of cases ($n = 20$, 44.4%) H&E was accompanied by another staining technique (in eight cases with Oil red O; in five with Sudan III; in four with Oil red O and Sudan III; in one with Osmium tetroxide; in one with Sudan IV, in one with Oil red O, Osmium tetroxide and thin-layer chromatography TLC); in another seven cases (15.5%), single staining different from H&E was used, while in three cases information about the technique used was not available (6.7%) (Figure 2).

In a single case, only radiological methods (non-contrast postmortem CT–PMCT) were used.[48] Other diagnostic techniques used included Fourier transform infrared microspectrophotometry + gas chromatography with mass spectrometry[49] and immunohistochemical application with anti-CD-61 and anti-fibrinogen[34,50] (Figures 3 and 4).

For postmortem radiological investigations, PMCT was used in three cases (6.7%) and more than one technique was used in five cases (11.1%) [in one case PMCT and postmortem computed tomography angiography (PMCTA)][51].

RESULTS FROM THE STUDIES INCLUDING RESEARCH PROGRAMMES

Cosmetic surgery

The combination of gluteal lipoinjection and liposuction has emerged as one of the most commonly performed procedures in cosmetic surgery.[47] Parallel to the increasing prevalence of such practices, there has been a rise in cases characterised by complications, including fatal outcomes.[52] The principal theory

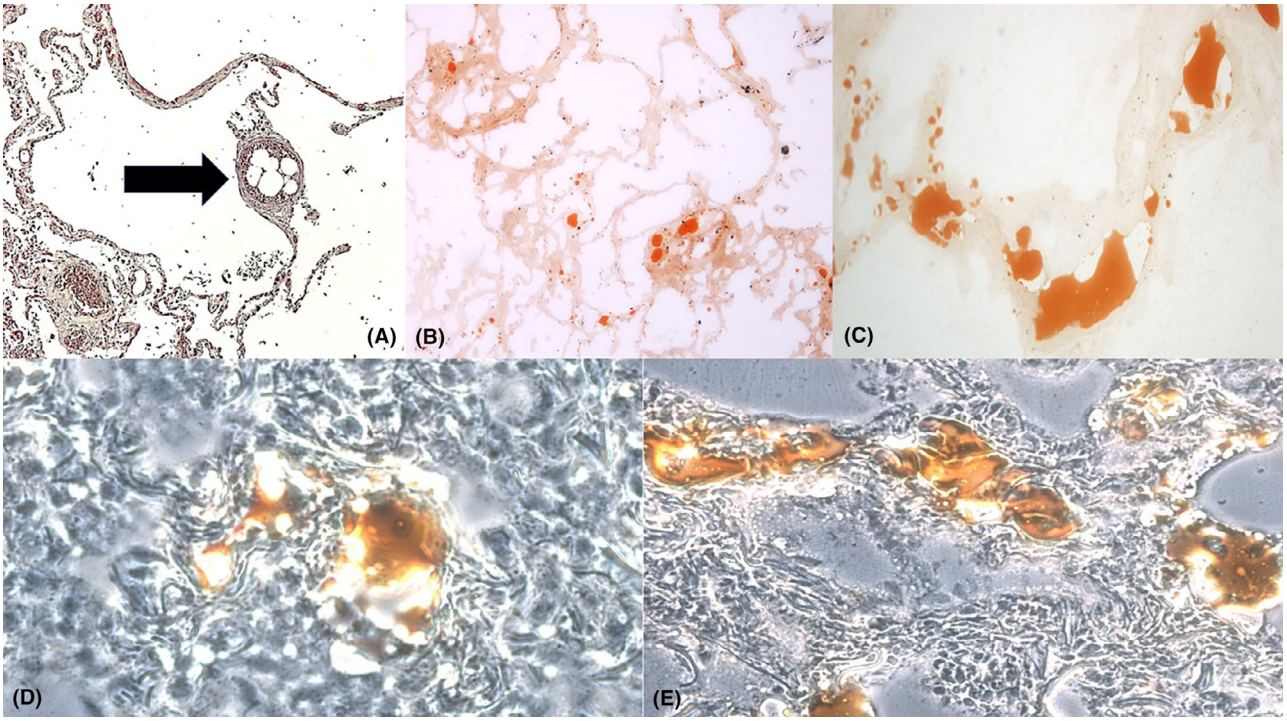

Figure 2. Examples of staining techniques. **A**, The appearance of lipid droplets within a pulmonary vessel as optically empty vacuoles (arrow). Haematoxylin and eosin. **B–E,** Pulmonary samples: fat emboli appeared as orange intravascular globules (**A**) (Sudan III × 20). When severe involvement was present, the fat emboli assumed elongated configurations within the vessels (**C**) (Sudan III × 60). The capillary of the pulmonary tissue filled with globular deposits of fat observed in phase contrast (**D**,**E**) (Sudan III × 200 and ×100, respectively).

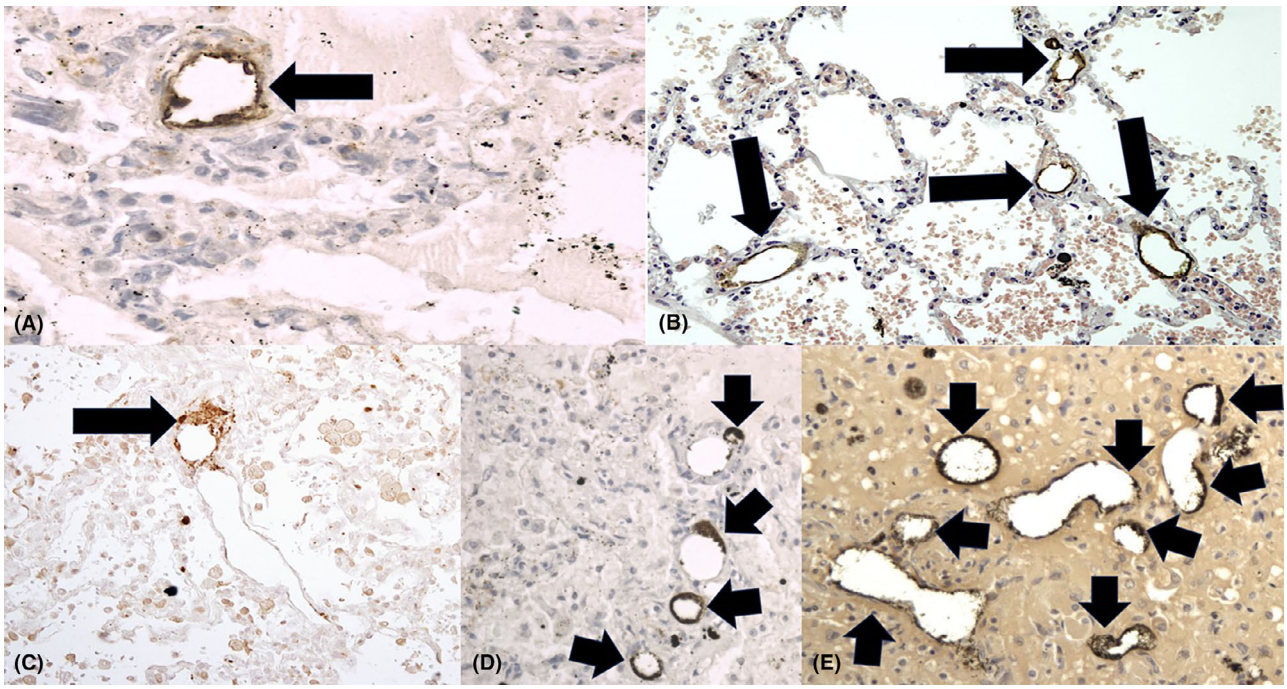

Figure 3. Examples of immunohistochemical application in cases of pulmonary fat embolism. **A**,**B**, Lung: fat globules (empty spaces) in a pulmonary vessel, positive (brown) reactions with platelets (CD61) surrounding empty spaces of fat embolisation (arrows) in the lung. **C**–**E**, Lung: reactions with fibrinogen (brown) surrounding empty spaces of fat embolisation (arrows).

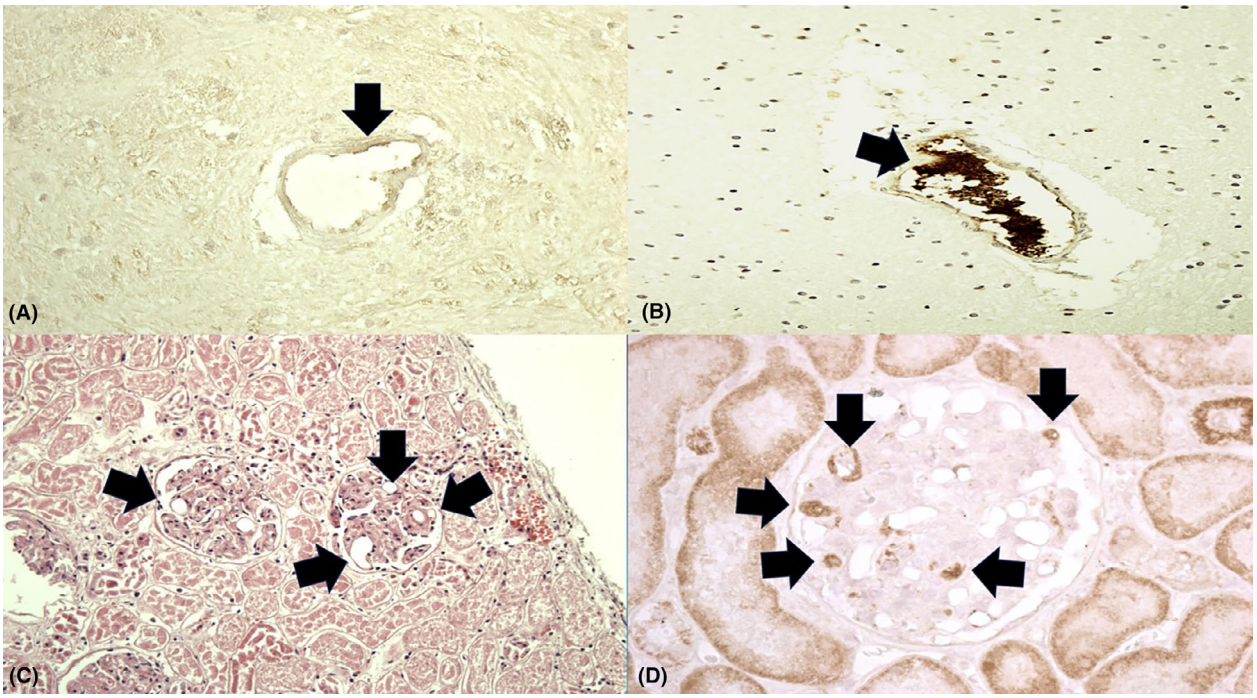

Figure 4. Examples of immunohistochemical application in cases of cerebral and kidney fat embolism. **A**, Brain: a slight layering of platelets (arrow) which delineates the boundaries of an entire intravascular void (CD61 ×100). **B**, Brain: reactions with fibrinogen (brown) delimiting empty spaces of fat embolisation (arrows). **C**,**D**, Glomerular capillaries: empty spaces representing fat emboli within the vessels. **C**, Haematoxylin and eosin and platelets (CD61) aggregates (brown) are sometimes stratified at the edge of the fat globules **D**, CD61.

regarding the cause of death is the injury to the gluteal vessels during surgery, resulting in the absorption of injected fat into the circulation, leading to pulmonary and cardiac complications.[47] To delve into the pathogenesis, Bayter-Marin *et al.*[53] retrospectively examined 16 cases of deaths secondary to gluteal lipoinjection, five during surgery and 11 after surgery. They did not find statistically significant differences in the general characteristics of the patients (age, body mass index), nor related to the volume of lipoinjection or liposuction (averaging 3117 cc and ~ 214 cc, respectively, in the examined cases). However, the studied cases presented common clinical characteristics such as hypoxaemia, hypotension and bradycardia. From the autopsy perspective, micro-embolism was present in all cases, while macroscopic FE was present in the lung, pulmonary vessels and cardiac vessels in 10 cases (62.5%). Regarding this last point, all patients who died immediately at the time of gluteal lipoinjection had macroscopic fat in their large pulmonary and cardiac vessels. The difference between macro- and micro-embolism also manifested in other organs, notably with the kidney and brain being more commonly affected in cases of macro-embolism.

On the same issue, in their retrospective study conducted through a survey completed by 413 plastic surgeons, Cárdenas-Camarena *et al.*[47] reported 64 deaths due to lipoinjection, including 14 cases involving liposuction and gluteal lipoinjection. For these latter cases, autopsy results highlighted FE as the cause of death in 13 cases and myocardial infarction in one case.

From the autopsy records of the National Institute of Legal Medicine and Forensic Sciences Regional Bogotá, nine cases of deaths between 1993 and 2008 emerged due to a combination of liposuction and lipoinjection (with an average of 3697 cc and 214 cc per buttock, respectively). FE was macroscopic in seven of the nine cases (77.7%) and microscopic in the remaining two cases (22.2%). Six deaths occurred during surgery (66.6%) and three (33.3%) within the first 18 h in the intensive care unit (ICU).

For such cosmetic procedures, a primarily mechanical pathogenesis has been proposed. The gluteal region, with its rich muscular vascularisation and the presence of large venous vessels (specifically, the gluteal vein in the subpiriformis or suprapiriformis channels), is particularly at risk for the embolisation of large amounts of fat, resulting in mechanical obstruction at the level of the heart and pulmonary vessels.[47]

Another increasingly popular procedure in recent years is autologous facial fat grafting.[54] Despite being considered a safe intervention, Dhooghe *et al.*[55] reported a case of a patient who died due to a massive cerebral micro-FE after facial fat grafting. The researchers then conducted a literature review, identifying 49 cases with similar events, six of which (12.2%) resulted in death.

Trauma and FE

The relationship between trauma and FE, particularly between the grade and extent of fractures and crushing of subcutaneous fatty tissue and the presence and severity of FES, has been studied by Bollinger *et al.*[56] They conducted a retrospective analysis of 50 victims of blunt trauma who had not undergone CPR and did not have cardiac damage severe enough to prevent fat particles from reaching the lungs. A moderately significant correlation ($r = 0.356$, $P < 0.05$) was found between the grade of PFE (according to Falzi grading) and fracture grade (no fracture, isolated, multiple/comminuted). However, there were no significant correlations between PFE and the severity of fractures (body regions affected by fractures and fracture grade) ($P = 0.170$), as well as survival time ($P = 0.567$), the amount of body regions affected by fat crushing ($P = 0.336$), fat crush grade ($P = 0.485$) and the amount of body regions affected by fractures.

The same study group[57] further investigated the correlation between PFE and survival time, extent of fat crushing, fat crush grade or number of body regions with fractures through the study of 188 non-resuscitated fatalities with blunt trauma and without right heart injury. The fracture grade ($r = 0.362$, $P = 0.000$), fracture severity ($r = 0.288$, $P = 0.000$) and the number of fractured regions ($r = 0.286$, $P = 0.003$) showed a strong correlation with the grade of PFE, while crushed body regions, crush grade and crush severity did not. A temporal correlation between survival time and PFE was observed only in the sense that very rapid deaths were often PFE-negative. Fatal PFE incidents were notably more prevalent in instances where survival time was less than 6 h (although not immediate). Additionally, occurrences of PFE grades 2 or higher were sporadically documented even 48 h following the incident.

Turkmen Samdanci *et al.*[58] conducted a retrospective evaluation of 402 cases diagnosed with isolated PFE (IPFE), among which the cause of death was traumatic (mainly due to traffic accidents) for 302 cases (75.1%) and atraumatic (mainly due to

myocardial infarction) for 100 cases (24.9%). CPR was performed for 177 traumatic cases (63.9%) and 100 non-traumatic cases (36.1%). The statistical analysis revealed that the percentage of grade 2-FE (according to the scoring system defined by Scully and Glass and modified by Mudd *et al.*[43]) was significantly higher in atraumatic cases compared to traumatic cases (respectively, $n = 100/100$ versus $n = 139/302$, $P < 0.001$). Conversely, grade 3-FE was significantly higher in traumatic IPFE cases compared to non-traumatic cases (respectively, $n = 150/302$ versus $n = 0/100$, $P < 0.001$). In none of the cases did the authors consider IPFE to be the main cause of death, but rather a contributing factor.

Non-traumatic FE

Farid *et al.*[59] investigated the relationship between bone marrow embolism (BME) and non-traumatic causes. In addition to routine H&E staining, the authors employed Martius scarlet blue trichrome stain to highlight fibrin and CD117 immunostains to accentuate haematopoietic progenitor cells. They reported eight cases of non-traumatic BME of the 11 cases where BME was present. Associations were found with mucinous carcinoma (1), hepatocellular carcinoma (1), severe congestion (2), liposuction (1), drug abuse (1), pulmonary hypertension (1) and heart failure (1).

Inoue *et al.*[60] investigated the relationship between PFE and heat exposure by selecting 54 cases of forensic autopsy cases, among which 25 (46.3%) exhibited PFE. Statistical analysis revealed an association between PFE and high ambient temperature (more than 40°C, resulting in a core body temperature of more than 39°C) [odds ratio (OR) = 4.6; 95% confidence interval (CI) = 1.2–21; $P = 0.03$].

Medical procedures

Among the confounding factors concerning the role of FE in determining death, one of the primary factors is autopsy findings following CPR manoeuvres. Specifically, manual chest compressions (mCC) or mechanical chest compression devices (ACCD) during CPR may lead to complications such as sternal or rib fractures which, in turn, can generate pulmonary bone marrow embolisms PBME and PFE.[61]

Eriksson *et al.*[14] investigated the incidence, time-course and severity of PFE and cerebral fat embolism (CFE) in trauma (due primarily to traffic accidents) and non-trauma patients at the time of autopsy, examining 50 cases. The cause of death was determined to be trauma in 68% ($n = 34$ of 50) of the decedents, with 88% ($n = 30$ of 34) experiencing blunt trauma and 12% (n = four of 34) experiencing penetrating trauma. While CFE was confirmed in only one patient with severe cervical spine and traumatic brain injury, PFE was detected in 28 of the 34 traumatically injured patients and in 10 of the 16 non-traumatic patients. CPR was performed in 30% of all cases, and 88% of non-trauma patients and 86% of trauma patients who received CPR had PFE.

In the traumatic group, CPR was performed in 21% (n = six of 28) of patients with PFE-positive compared to 17% (n = one of six) of patients without PFE. In the group of medically deceased individuals, PFE occurred in 70% of patients who received CPR (n = seven of 10) and in 17% of patients who did not receive CPR (n = one of six).

Among the group of traumatically injured patients with PFE, there was no significant difference regarding patient characteristics and types of injuries. All patients who survived longer than 60 min (n = four of four) had evidence of PFE, whereas 80% ($n = 24$ of 30) of patients who died within 60 min of injury had evidence of PFE.

The prevalence of PFE among cadavers received at the morgue, as well as the relationship between PFE and CPR, was investigated by Voisard *et al.*,[36] who analysed lung tissue samples from 256 consecutive cadavers admitted to the morgue.

PFE was detected in 54% of all cases with trauma (excluding CPR), 58% of all cases with CPR (excluding trauma) and 10% of all cases without CPR or trauma. The authors observed a significant positive correlation between trauma and PFE ($\chi^2 = 77.49$; $P < 0.0001$) as well as between CPR and PFE ($\chi^2 = 64.96$; $P < 0.0001$), confirming the association between the presence of PFE and antemortem exposure to trauma (mechanical trauma or CPR).

The severity of PFE was significantly higher in the 71–90 years age group compared to individuals aged < 70 years. This finding may be explained by the increased mineralisation and higher risk of fractures in the bones of elderly individuals.

Only 11 cases presented Falzi-grade III PFE, which could potentially be identified as a cause of death: six of these cases involved blunt trauma, while five cases only involved CPR, but all individuals died of natural causes.

Neither gender nor the degree of putrefaction had a significant impact on the incidence of PFE.

In order to analyse the frequency and intensity with which CPR manoeuvres are associated with PBME and PFE in non-traumatic cardiac arrest cases, Ondruschka *et al.*[62] studied three groups of 15 individuals each (groups 'ACCD', 'mCC' and 'no CPR').

They found that most cases did not exhibit signs of PBME (20.0% PBME-positive for the ACCD group and 26.7% PBME-positive for the mCC group). PBME appeared to be mainly diffusely distributed throughout the lung parenchyma at relatively low rates, with 3–19% of vessel lumens showing barotrauma positivity, regardless of the CPR method used. Similar prevalence percentages were also recorded for low-grade PFE (according to Falzi's classification): mild pulmonary FE (grade I) was diagnosed in 20.0% of the ACCD group and 13.3% of the mCC group, while distinct (grade II) or massive (grade III) PFE was not detected in any of the observed cases. These results suggest that both PBME and PFE can be encountered relatively frequently in autopsy settings following CPR (together with sternal and rib fractures) in non-traumatic causes of death, but cannot be considered causative factors for death.

On the same topic, Rudinská *et al.*[63] conducted a prospective cohort study involving 106 non-survivors following CPR due to out-of-hospital cardiac arrest. Despite the particularly high rates of traumatic injuries from CPR (sternal fractures in 66.9%, rib fractures in 80.2% and serious intra-thoracic injuries in 34.9% of cases, with a median number of rib fractures of 10.2 fractures per person), PFE was not found to be the cause of death in any case (PFE grade IV was listed as a contributing factor to death in specific cases studied).

Compared to the Ondrushka study, a higher prevalence rate of PFE was observed ($n = 40$, 37.7% of total cases), predominantly of low grade, resulting in grades III and IV, according to the adopted grading system, in only five cases each.

The relationship between FE and infusion by intra-osseous catheter (IIC) was addressed in a study by Castiglioni *et al.*[64] through a retrospective study of 20 cases of paediatric deaths autopsied. All subjects had received CPR without bone fractures or other possible causes of PFE. Two groups were compared: 13 cases with IIC (group A) and seven cases without IIC (group B).

A significant difference in the prevalence of PFE between the two groups emerged. PFE was identified in eight cases within group A, comprising four cases with a Falzi score of I and four cases with a Falzi score of II. Conversely, no instances of PFE were observed in group B.

These data confirmed IIC as a possible aetiological cause of PFE, while no correlation was found between PFE and other factors such as age or the number of intraosseous catheters.

Other interventions particularly at risk are represented by orthopaedic procedures. de Froidmont *et al.*[65] investigated the relationship between FE and bone cement implantation syndrome. A sample of six subjects who underwent cemented total hip arthroplasty due to acute femoral neck fracture was compared with 44 other individuals who died after other injuries and/or interventions. The samples were studied through both autopsy and radiological and histological investigations. PFE was found to be the cause of death in all six cases who died intra-operatively, representing the most important factor responsible for severe cardiorespiratory function deterioration during cemented arthroplasty. Indeed, it was considered one of several lethal mechanisms in 16 road-traffic victims with rapid respiratory function deterioration. PFE was not reported in the other cases (16 cases of trauma with haemodynamic instability and respiratory function deterioration; eight cases with contrast medium administration; four cases with cemented total hip arthroplasty for osteoarthritis and decompressive laminectomy).

Paediatric cases

Eriksson *et al.*[14] conducted a retrospective analysis of 67 deceased paediatric patients (≤ 10 years), where four groups were identified based on the cause of death, consisting of trauma ($n = 21$ of 67; blunt $n = 17$, penetrating $n = 4$), drowning ($n = 14$ of 67), burn (n = seven of 67) and medical ($n = 25$ of 67). PFE, CFE and kidney fat embolism (KFE) were present in 30, 15 and 3% of all patients, respectively, suggesting that they are not rare findings in paediatric trauma and medical deaths.

The incidence of PFE was not significantly different by cause of death and was found to be related to a higher BMI. Specimens were also evaluated for the presence of haematopoietic cell lines, but none of the samples evaluated in any organ system demonstrated nuclear elements suggestive of being of BM origin. Among other findings, 71% of patients with CFE did not have a PFO; one individual had both PFE and CFE, while six individuals had CFE without PFE and 15 individuals had PFE without CFE.

Radiology

The utility of PMCT for diagnosing PFE was studied by Chatzaraki *et al.*[66] They compared autopsy results and PMCT images of the pulmonary trunk and the right and left pulmonary arteries to search for fat layers in a group of 366 cases PFE-positive according to histology (classified according to the Falzi grading) with a group of 464 PFE-negative controls.

Fat layers in the pulmonary vessels on PMCT were detected in 18 cases. Among these, two belonged to

the control group (0.4% within the control group) and 16 to the PFE group (4.4% within the case group) (χ^2, $P < 0.001$). The presence of fat layers was statistically higher in the PFE group of Falzi grade ≥ 2.5 compared with the PFE group of grade ≤ 2 (χ^2, $P < 0.001$). They concluded that PMCT showed low sensitivity (4.37%) but very high specificity (99.57%) for the diagnosis of PFE independent of grade.

Makino *et al.*[67] also analysed the utility of PMCT and postmortem magnetic resonance (PMMR), studying 27 forensic autopsy cases, of which three presented a massive FE (Falzi grade III) on histology. For the latter cases, PMCT detected a 'fat-fluid level' in the right heart or intraluminal fat in the pulmonary arterial branches in two subjects, while PMMR detected these findings more clearly in both subjects. In one of the three subjects, both PMCT and PMMR were negative. Finally, there were no positive findings on PMCT and PMMR in the 24 control subjects.

Histology and technological innovation

Turillazzi *et al.*[37] retrospectively evaluated the clinical data and autopsy records of 2.738 autopsies, identifying 21 cases in which FES was determined as the cause of death, occurring in patients with major trauma and long bone traumatic fractures. This group was compared with 21 fatal cases of major trauma where the cause of death was not attributed to FE, as well as with 47 fatal cases serving as a control group.

In each case, five tissue samples were obtained from the lungs, comprising one piece from each lobe. These samples were stained with Sudan III. Upon confirmation of positivity, the samples underwent further quantitative analysis. The area of each pulmonary slide was measured in square millimetres using a colour video camera interfaced with a light microscope and digitalised. Three-dimensional images of histological sections on confocal laser scanning microscopy were recorded, and the reconstruction of fat emboli was obtained from the Z-lines cut surface. During this process, the number of fat emboli present was tallied and normalised to 100 mm^2. The mean and total size of fat emboli were subsequently discerned and calculated as a percentage of the total lung area under examination.

In summary, the main findings of the study were: (i) the variability of the total number of emboli, influenced by the magnification rate of the image-acquiring system; (ii) the unreliability of the mean size of the emboli (mean area per mm^2); (iii) the usefulness of the total and mean area of the emboli, even though it strictly depends on the areas of the histological specimens selected and analysed; and (iv) the gold standard of two parameters: the total percentage of embolised tissue area, compared with the mean percentage of embolised tissue area and the embolised tissue area compared with the total tissue area for each sample. The authors stated that these latter parameters truly express the degree and spread of FE, in addition to showing a good correlation with the clinical presentation.

Cheng *et al.*[68] investigated the specificity of Fourier transform-infrared (FT-IR) for detecting PFE through the study of 30 formalin-fixed human lung tissue and adipose tissue specimens, comprising 15 positive and 15 negative for PFE. FT-IR-based diagnosis for FE exhibited less accuracy than Oil red O staining (positive accuracy = 14 of 15 versus 15 of 15, respectively). However, the authors suggest that FT-IR could remain an operationally simple and immediate method, as well as being non-destructive to the samples used. Any future refinement of the method may ensure wider adoption.

Pathophysiology

Fracasso *et al.*[69] sought to define the involvement of the right ventricle in cases of PFE through an immunohistochemical investigation using the markers fibronectin and C5b-9.

They studied 21 cases of polytrauma with bone fractures (mean age 64.6 years), comparing them with a control group of 21 forensic cases with various causes of death (mean age 68.6 years). Both ventricles were studied in all cases.

The comparison of the grade of necrosis in the right ventricles showed prevalent ischaemic damage in the FE group with the antibody fibronectin ($P = 0.0014$), while no significant differences emerged with the antibody C5b-9 ($P = 0.1301$).

The comparison of the grade of necrosis in the left ventricles showed a prevalent involvement of this ventricle in the control group with both antibodies (fibronectin, $P < 0.0001$; C5b-9, $P = 0.0063$).

The comparison of the difference in the grade of necrosis between the right and left ventricle (Δfibronectin and ΔC5b-9) in the two groups showed a statistically significant difference between the study and control group with both antibodies (fibronectin, $P < 0.0001$; C5b-9, $P < 0.0095$).

These data indicate the potential primary involvement of the right ventricle and its failure. However, the authors do not provide information on whether CPR was performed on the subjects included in the study, nor do they list prior resuscitation as an

exclusion criterion. Therefore, it is not possible to rule out that the findings related to the cardiac ventricles may be due to CPR rather than FE.

However, these results were not replicated by the same group in a larger study[70] where, of 52 cases of PFE, prevalent right ventricular damage did not emerge in cases of high-degree PFE, as in the previous investigation.

Patent foramen ovale

The role of PFO in the pathogenesis of PFE was studied by Nikolic *et al.*[8] in a prospective autopsy study. In this study, 32 subjects with a sealed foramen ovale (SFO) and 20 individuals with PFO, both suffering from orthopaedic blunt injuries and consequent PFE, were involved. They found no difference in either the incidence of KFE in subjects with PFO compared to those with SFO (Fisher's exact test 0.228, $P = 0.154$) or in the grade of KFE (Pearson χ^2 2.728, $P = 0.435$). Therefore, the role of PFO was considered non-crucial in facilitating the development of systemic FE. The authors suggested that arteriovenous shunts and connections between the functional and nutritive circulatory systems within the lungs may have a greater impact than a PFO in promoting the occurrence of systemic FE in individuals with femoral fractures.

Discussion

The present systematic review highlighted that research on FE, both in terms of its aetiopathogenesis and diagnosis, is current among various specialised fields and forensic pathology. The systematic analysis of case reports revealed that FE is a topic of forensic interest in both traumatic and non-traumatic cases. The latter, which constitute the majority of the analysed case series during the past 30 years, are mainly related to surgical procedures, primarily orthopaedic (involving segments particularly rich in BM) and cosmetic surgeries.

FE is an important topic in forensic pathology, particularly concerning issues of professional liability. Of particular interest are cosmetic procedures, where non-medical or unlicensed individuals often operate. Our analysis revealed cases involving the injection of autologous skin tissue, as well as instances where non-professional operators injected unconventional or particularly dangerous substances, e.g. vitamin E and corn oil.[21,49]

Orthopaedic procedures also carry risks, including bone cement implantation, total hip arthroplasty,[71] the Ilizarov procedure,[72] muscle-release and tenotomy[73] and spinal surgeries.[50]

Although some medical causes described in the past, such as pancreatitis, have not been observed in more recent case reports, others, such as sickle cell disease,[74–76] should draw the attention of clinicians and pathologists as potential causes of BM infarctions.

In the presentation of case reports, a critical issue has been the lack of complete and detailed information on the premortem clinical conditions. In the majority of studies ($n = 40$, 88.9%), including those where a diagnosis of FES was made, clinical criteria supporting the diagnosis were not reported.

While such information is often lacking in cases where subjects die or enter critical conditions outside medical observation, it is also insufficient in reports where the patient was hospitalised. Diagnostic criteria for FES, moreover, do not seem to be used pre-emptively for timely diagnosis; instead, they are often reconstructed postmortem during autopsy, together with the retrieval of clinical records, to support the diagnosis of FES.

Greater attention should be given by clinicians and healthcare providers who come into contact with critical patients. In cases of traumatic events or high-risk surgical procedures, specific diagnostic criteria for FES should be actively sought and documented in an assessment form. This would enable the forensic pathologist to identify the organs potentially affected more precisely by FE and the origin site of the embolism.

Another clinical aspect we focused upon is the issue of sudden thrombocytopaenia. This criterion is particularly challenging, as it can be confused with a haemorrhagic event in the differential diagnosis, leading to potential diagnostic and therapeutic errors. Data on this aspect were only provided by a limited number of studies, preventing the detection of statistically significant results.

An open issue, and a potential confounding factor, was the relationship between CPR and FE. As observed from the case analysis (where CPR was performed in nearly two-thirds of the sample), CPR procedures are common, especially in non-traumatic cases where contact with healthcare providers can be more immediate. The study by Ondruschka *et al.*[62] found that pulmonary embolisms from BM or lipids can be encountered relatively frequently in autopsy settings following CPR in non-traumatic causes of death, but they are not considered a determining factor. Similarly, the study by Rudinská *et al.*[63] agrees to consider CPR as secondary to the possibility of

generating PFE. Although there are no conclusive studies, several factors suggest a causal link between FE and CPR: (i) a survival time too short (less than tens of minutes or a few hours required for the development of FES); (ii) the presence of sternal and rib fractures observed during gross examination; and (iii) histologically, the presence of BME and a low grade on the chosen grading system.

It remains to be established whether the IIC, a possible cause of PFE as shown by the study of Castiglioni *et al.*,[64] also represents a potential cause of death, especially in paediatric cases. Paediatric defects in the closure of the foramen ovale have been implicated in the mechanical theory of FE. However, the study by Nikolic *et al.*[8] has downplayed the potential causality of this condition in determining the systemic spread of FE.

Another critical point highlighted by the study is the underutilisation of grading systems, with their explicit application noted in just under half of the case reports. Despite some limitations of the method as noted in the literature,[37] the Falzi methodology remains the most widely used.

Regarding staining techniques, H&E is often accompanied by other more specific colourations, particularly Oil red O or Sudan III. Other diagnostic techniques, such as Fourier transform infrared,[49,68] are still experimental.

Of interest, albeit currently anecdotal, is the application of immunohistochemical techniques with anti-CD61 and anti-fibrinogen.[34,50] These methods, however, have the advantage of potentially aiding diagnosis where samples (as in the case of staining with H&E) have been treated with solvents that have removed lipid components.

Postmortem radiological investigations, such as PMCT, PMCTA and PMMR, remain underutilised. Notably, the limited sensitivity of PMCT[66] and certain challenges associated with PMMR[67] have been highlighted.

These data underscore the primacy of autopsy examination and histopathological investigation in diagnosing FE. However, as observed in case reports, investigations are often conducted without standardised procedures, with some discretion and heterogeneity in the choice of organs for histological study, staining techniques and ancillary investigations.

Finally, from a pathophysiological perspective, although nearly a century has passed since the initial publications on the biochemical theory of FE, no conclusive studies on this topic have been identified. The heterogeneity of non-traumatic cases, which this theory primarily addresses, further complicates the ability to conduct systematic studies.

Conclusions

Throughout this study, we aimed to compile all case reports and experimental studies related to FE reported in the literature during the past 30 years. This endeavour allowed us to elucidate the operational procedures adopted by forensic pathologists in handling FE cases and to address contentious issues concerning both diagnostic aspects and the role of FE as a causal mechanism of death.

Our study is subject to inherent limitations regarding the reported case data. Precise determination of FE prevalence across various specialties is hindered by the discretionary nature of case report documentation. Nevertheless, despite this limitation, our study, albeit lacking statistical validity, identified a prevalent reporting trend in traumatic and surgical cases, particularly in orthopaedics, consistent with existing literature. Notably, among non-traumatic FE causes, cosmetic surgery emerged as a significant factor. Publisher selection bias favouring more intriguing and contemporary findings may represent a potential confounding factor.

However, our study also sought to contribute contemporary insights into the field of FE, highlighting novel procedures deserving attention by forensic pathologists. It is important to acknowledge the heterogeneity observed in the reported works, both in terms of case reporting and experimental methodologies. Nonetheless, through this study we endeavoured to provide a comprehensive overview of the FE topic, furnishing forensic pathologists with an updated overview useful for clinical practice and guiding future research trends, as well as the development of standardised procedure.

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Conflicts of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Non-traumatic cases.

Table S2. Traumatic cases, and a List of the included and excluded studies are reported in supplementary data.