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Research Article

Association of Retinal Microvascular Changes, Hematological Abnormalities, and Renal Dysfunction with Pulmonary Complications Following Traumatic Long-Bone Fractures: A Prospective Medico-Legal Cohort Study

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ABSTRACT

Background: Microvascular injury, hematological abnormalities and impaired renal function are potential accompaniments of pulmonary complications following traumatic long-bone fracture. These early findings have associations with later respiratory morbidity, which should be explored.

Objective: To examine associations of early retinal microvascular abnormalities, hematological disturbances, and reduced renal function with pulmonary complications within seven days of traumatic long-bone fractures.

Methods: This prospective multicentre cohort comprised 120 adults with traumatic long-bone fractures treated at participating hospitals in Pakistan from January 2025 to January 2026. Baseline measurements comprised retinal examination, hematological indices, estimated glomerular filtration rate, and injury severity. Pulmonary complications were evaluated within 7 days of occurrence. Association was tested by logistic regression (adjusted for age and severity of injury).

Results: Pulmonary complications occurred in 28 patients (23.3%). The composite endpoint included pneumonia, ARDS, pulmonary thromboembolism, and hypoxemic respiratory failure. Retinal abnormality was found in 15 patients (12.5%), thrombocytopenia in 33 patients (27.5%), and decreased estimated glomerular filtration rate (eGFR) in 18 patients (15.0%). There was a higher prevalence of pulmonary complications among patients with retinal abnormalities (60.0 % vs. 18.1 %), as well as in patients with thrombocytopenia (42.4 % vs. 16.1 %) and reduced renal function (50.0 % vs. 18.6 %). Retinal abnormalities (adjusted OR [aOR] 5.27; 95% CI, 1.25 to 22.24) and thrombocytopenia (aOR 3.39; 95% CI, 1.12 to 10.28) continued to be associated with pulmonary complications in the exploratory multivariable model. This association was not statistically significant after adjustment (aOR 2.51; 95% CI 0.65–9.69). The rate of pulmonary complications rose from 8.6% in patients with none of the three abnormalities to 69.2% in patients with two or more of the three abnormalities.

Conclusion: Microvascular changes in the retina were correlated with increased pulmonary morbidity within the first seven days following long bone fracture and the presence of thrombocytopenia. These findings are useful for integrated clinical assessment and systematic medico-legal documentation; the incremental prognostic value of these markers will be validated by external sources.

Keywords: Long-Bone Fractures, Retinal Microvascular Abnormalities, Thrombocytopenia, Renal Dysfunction, Pulmonary Complications, Medico-Legal Assessment, Prospective Cohort Study.

INTRODUCTION

Traumatic long-bone fractures represent a major cause of injury-related morbidity and are frequently associated with high-energy mechanisms, including road traffic accidents, occupational injuries, and falls from height[1]. While stabilization and restoration of function are the main aims of orthopedic trauma, systemic complications can have a significant impact on outcomes. Respiratory deterioration, prolonged hospital stay, and increased critical-care needs are a result of pulmonary complications such as fat embolism syndrome (FES), acute respiratory distress syndrome

(ARDS), pulmonary thromboembolism, and pneumonia[2]. Mechanisms include mechanical embolisation, systemic inflammatory response, endothelial injury, and microcirculatory disturbances. These complications are not always present, and their severity depends on fracture type, other injuries and physiological state of the patient. The early detection of clinical and biochemical abnormalities that are related to pulmonary deterioration is, therefore, important for the improved assessment and management following trauma[3].

Retinal microvascular changes are a potential source of information regarding systemic vascular changes after significant skeletal trauma. Microvascular occlusion, endothelial dysfunction, and ischemic damage of the retina from circulating embolic material and inflammatory mediators are especially vulnerable[4]. Cotton-wool spots, intraretinal hemorrhages, and Purtscher-type retinal whitening have been reported after long bone fractures and other serious traumatic injuries. Miguel et al. illustrated the clinical relevance of microvascular changes in the retina in cases of Purtscher's and Purtscher-like retinopathy, and further studies have clarified the relationship between traumatic and systemic diseases. But these abnormalities are not unique to fat embolism, and the association with subsequent pulmonary abnormalities is not fully understood. The evaluation of microvascular alterations in the retina may give further information on the microvascular disturbances associated with skeletal trauma[5,6].

Another important aspect of the systemic physiological reaction to traumatic fractures is the hematological abnormalities. Acute tissue injury can initiate inflammatory and coagulation reactions, which can lead to consumption of platelets, changes in circulating blood cell populations, and disturbances in hemostatic regulation[7]. Thrombocytopenia and anemia are of special interest since they can indicate a bleeding or hemodilution effect, inflammatory processes, or coagulopathy associated with trauma. In addition to hemostasis, platelets play a role in inflammatory signaling, endothelial interaction, and microvascular regulation, which may lead to pulmonary vascular dysfunction[8]. Previous studies have shown that there is a correlation between post-traumatic thrombocytopenia and organ dysfunction, but individual organ systems and clinical populations differ in these relationships. These findings highlight the need for assessing the hematological changes in the context of other markers of systemic injury in the evaluation of pulmonary complications after long-bone fractures[9-12].

The other sign of systemic physiological disruption which happens after large trauma is renal dysfunction. The renal dysfunction that occurs in the early post-traumatic period may be caused by the action of inflammatory mediators, endothelial damage, tissue hypoperfusion and/or hemodynamic instability[12,13]. The relationship between renal and pulmonary dysfunction is now recognized and believed to be mediated by "lung–kidney crosstalk", involving inflammatory signaling, vascular permeability, oxidative stress and fluid disturbances. Renal dysfunction can also be a component of a more generalized reaction to injury, and alterations in renal clearance and fluid control can also affect pulmonary physiology. However, early abnormalities in renal function can also be the result of pre-existing disease, dehydration or changes in status as a result of resuscitation. Hence, their association with subsequent lung complications needs to be carefully evaluated considering injury severity and other suitable clinical characteristics[14,15].

There are also important medico-legal implications of the systemic effects of long bone traumatic fracture. It is important to differentiate between the primary traumatic lesion and complications that occur on the way to determine the full extent of the trauma[16]. The severity and consequences of an injury may be impacted by pulmonary deterioration, hematological disturbances, renal impairment, prolonged hospitalization and intensive-care requirements. Then, a proper chronological record, objective clinical findings, laboratory investigations and radiological evidence are required in the context of a thorough medico-legal investigation. Systematic abnormalities in identification could aid and validate medical data for the reconstruction of the course of post-traumatic complications. However, the presence of an associated abnormality is not in and of itself sufficient to establish the precise mechanism of injury, individual causation, or legal responsibility. The combination of a multi-disciplinary clinical evaluation and a uniform medico-legal record may facilitate more thorough, reproducible and interpretable documentation of the medical evidence relating to an injury[7,16].

Although the association with multisystem involvement is now well recognized in the aftermath of orthopedic trauma, the association

of retinal microvascular changes, hematological abnormalities, and renal dysfunction with subsequent pulmonary involvement is still not well described[18-20]. Past studies have focused on organ presentation, diagnosis of FES, or systemic complications and complications in heterogeneous trauma patient populations. The clinical significance of the retinal, haematological and renal abnormalities in this patient group and their relevance to medico-legal documentation has been little studied. The present study was designed to identify the correlation between retinal microvascular changes, haematological abnormalities and renal dysfunction with the pulmonary complications after traumatic long bone fractures. Secondary aims included assessment of the association of concurrent systemic abnormalities with respiratory morbidity, and the importance of detailed clinical examination for medico-legal purposes for post-traumatic complications.

MATERIALS AND METHODS

Study Design and Setting

The study was a multi-centre prospective cohort study, carried out at Faisalabad Medical University and its Allied Hospitals I and II, Faisalabad, Pakistan, and the Department of Orthopedic Surgery, Nawaz Sharif Medical College, Aziz Bhatti Shaheed Teaching Hospital, Gujrat, Pakistan, from January 2025 to January 2026. The total population included 120 adults with long bone fractures caused by trauma. Association between early abnormalities of the retina, haematology and kidneys with late pulmonary complications was analysed. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used as a guide to reporting[8].

Study Population and Eligibility Criteria

All adult (18 years and above) patients with radiographically confirmed traumatic lower femur, tibia and humerus fractures were included. Eligible patients were those who presented within 24 hours of injury with one or more long bone fractures. Any major direct trauma to the thorax, pulmonary complications at presentation, advanced pre-existing retinal disease, dialysis-dependent renal failure, and conditions which precluded a reliable baseline assessment were excluded. In the eligible participants, a standard clinical and laboratory evaluation was carried out.

Clinical and Ophthalmological Assessment

Demographic data, mechanism of injury, fracture site, associated injuries, and physiological parameters were evaluated as the baseline data. Fracture characteristics were assessed by clinical examination and radiological investigation, and severity of injuries was assessed using the Injury Severity Score (ISS)[9]. Details of fracture fixation, surgery, and treatment needs were documented.

Fundoscopy was carried out within 24 hours of presentation, and if possible, photographs of the retina were obtained. Retinal microvascular abnormalities were described based on their morphology and distribution, such as cotton wool spots, retinal hemorrhages, and purtscher type retinal whitening. The examination was able to distinguish the acute post-traumatic microvascular changes from the changes of pre-existing retinal disease.

Hematologic and Renal Evaluation

Initial blood parameters included concentration of hemoglobin, hematocrit, leucocyte count, and platelet count. Thrombocytopenia was defined as platelet count < 150 × 109/L; anemia was defined as hemoglobin threshold < sex specific threshold. Hematological parameters were compared with the severity of the injury and respiratory outcome in each patient.

Renal function assessment was done using serum creatinine and estimated glomerular filtration rate (eGFR) using the CKD-EPI 2021 equation. Renal function was defined as reduced if eGFR was below 60 mL/min/1.73 m². In the presence of more than one serum creatinine value, acute kidney injury (AKI) was defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Pulmonary Complication Assessment

The first seven days after injury were used for patients who were at risk for pulmonary complications. Respiratory evaluation consisted of clinical examination, peripheral oxygen saturation, chest radiography, and other investigations as needed. Refractory ARDS, pneumonia, pulmonary thromboembolism, or clinically important respiratory failure (as measured by blood gases and oxygen saturation) was the major endpoint.

Acute respiratory distress syndrome was diagnosed as per the current basic definition worldwide. Not only were the clinical and radiographic features compatible with the diagnosis, but pulmonary thromboembolism

also had to be confirmed by appropriate imaging, and the same was true for the diagnosis of pneumonia. A differential diagnosis was fat embolism syndrome. The pulmonary outcome definition was intentionally designed to exclude retinal and haematological abnormalities, so as not to overlap with the classification of the outcome.

Medico-Legal Assessment

Medico-legal evaluation was performed based on the status of injury, anatomic characteristics of fracture, severity of trauma and chronological progression of systemic complications. To distinguish between primary traumatic injuries and those that developed later in the course of treatment, documentation of clinical findings, laboratory investigations, imaging results, deterioration in respiratory function, and requirement for intensive care were used. The emphasis of the assessment was on the time course of the primary injury and clinical events that ensued, as well as objective record of morbidity related to the primary injury.

Statistical Analysis

Categorical variables were presented as frequencies and percentages and continuous variables as means and standard deviations or as median and interquartile ranges as appropriate. Chi-square test or Fisher's exact test was used to compare categorical variables, and independent-samples t-test or Mann–Whitney U test to compare continuous variables between groups.

Association of retinal microvascular abnormalities with thrombocytopenia, reduced eGFR, and pulmonary complications was assessed using logistic regression. Adjustment variables included age and injury severity, and the number of covariates was considered with regard to the observed pulmonary events. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Two-sided p-values < 0.05 were considered statistically significant.

Ethical Considerations

The study has been performed in compliance with the ethical principles of the Declaration of Helsinki and the institutional and national research ethics rules. The study was undertaken with the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) approval. Informed consent was obtained. Throughout the research process, participants' privacy, confidentiality, and data protection have been maintained. Research data were kept securely, seen only by authorized people, and used only for approved research purposes. Due consideration was given to the rights, safety, and welfare of participants in all study procedures.

RESULTS

Baseline Demographic and Clinical Characteristics

The total number of patients studied was 120; 90 (75.0%) patients were males and 30 (25%) patients were females, all had long-bone fractures due to trauma. The mean age was 39.1 ± 12.8 years. The most common mechanism of injury was road traffic accidents (64.2%), followed by falls (24.2%) and occupational injuries (11.7%). The most common fractures were of the femur (56.7%), tibia (32.5%), and humerus (10.8%). Twenty patients (16.7%) had multiple fractures of long bones. Of these, 28 patients (23.3%) developed a pulmonary complication within 7 days, and the other 92 (76.7%) were not considered to have the primary outcome. Patients who developed pulmonary complications were older and had a higher median anatomical injury severity (Injury Severity Score [ISS]) of 25.5 compared to 15.0 when patients did not develop such complications. Demographic and injury-related characteristics of baseline data are found in Table 1.

Table 1. Baseline demographic and clinical characteristics according to pulmonary complication status

Characteristics	Total (n=120)	Pulmonary complications (n=28)	No complications (n=92)
Age, years, mean ± SD	39.1 ± 12.8	45.5 ± 10.9	37.1 ± 12.7
Male	90 (75.0)	21 (75.0)	69 (75.0)
Female	30 (25.0)	7 (25.0)	23 (25.0)
ISS, median (IQR)	17.0 (12.0–23.0)	25.5 (20.3–28.8)	15.0 (11.0–21.0)
Mechanism of injury			
Road traffic accident	77 (64.2)	18 (64.3)	59 (64.1)

Fall	29 (24.2)	7 (25.0)	22 (23.9)
Occupational injury	14 (11.7)	3 (10.7)	11 (12.0)
Principal fracture location			
Femur	68 (56.7)	17 (60.7)	51 (55.4)
Tibia	39 (32.5)	9 (32.1)	30 (32.6)
Humerus	13 (10.8)	2 (7.1)	11 (12.0)
Multiple long-bone fractures	20 (16.7)	8 (28.6)	12 (13.0)

Values are expressed as n (%) unless otherwise specified. Percentages in outcome columns are calculated using their respective group denominators. SD, standard deviation; IQR, interquartile range; ISS, Injury Severity Score. Principal fracture location and multiple-fracture status are separate classifications.

Retinal Microvascular Changes and Pulmonary Complications

Retinal microvascular abnormalities were identified in 15 patients (12.5%) during the initial ophthalmological assessment. Cotton-wool spots were the most frequently observed findings, followed by intraretinal hemorrhages and Purtscher-type retinal whitening. Pulmonary complications subsequently developed in nine of the 15 patients with retinal abnormalities (60.0%), compared with 19 of 105 patients (18.1%) without these findings. Patients with retinal microvascular abnormalities had higher odds of pulmonary complications (OR 6.79; 95% CI 2.16–21.36; p=0.001). The corresponding frequencies and effect estimates are presented in Table 2.

Hematological Abnormalities and Pulmonary Complications

Thrombocytopenia was identified in 33 patients (27.5%), while anemia was observed in 47 (39.2%). Pulmonary complications occurred in 14 of 33 patients with thrombocytopenia (42.4%), compared with 14 of 87 patients (16.1%) with platelet counts within or above the predefined threshold. Thrombocytopenia was associated with greater odds of pulmonary complications (OR 3.84; 95% CI 1.57–9.42; p=0.004). Among patients with anemia, 14 of 47 (29.8%) developed pulmonary complications, compared with 14 of 73 (19.2%) without anemia. However, this association did not reach statistical significance (OR 1.79; 95% CI 0.76–4.20; p=0.192). The unadjusted association was more pronounced for thrombocytopenia than for anemia (Table 2).

Renal Dysfunction and Pulmonary Complications

Reduced baseline renal function, defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m², was identified in 18 patients (15.0%). Pulmonary complications occurred in nine of these patients (50.0%), compared with 19 of 102 patients (18.6%) with preserved baseline eGFR. Reduced renal function was significantly associated with subsequent pulmonary complications in unadjusted analysis (OR 4.37; 95% CI 1.53–12.48; p=0.012). Adjusted analyses additionally accounted for age, anatomical injury severity, and the other measured systemic abnormalities (Tables 2 and 3).

Table 2. Associations of Early Systemic Abnormalities with Pulmonary Complications

Baseline variable	Patients with abnormality, n	Pulmonary complications, n/N (%)	Unadjusted OR (95% CI)	p-value
Retinal microvascular abnormalities	15	9/15 (60.0)	6.79 (2.16–21.36)	0.001
Thrombocytopenia	33	14/33 (42.4)	3.84 (1.57–9.42)	0.004
Anemia	47	14/47 (29.8)	1.79 (0.76–4.20)	0.192
Reduced eGFR	18	9/18 (50.0)	4.37 (1.53–12.48)	0.012

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate. Each odds ratio compares patients with the specified abnormality against those without it. Confidence intervals were calculated using conventional logistic odds-ratio estimation, and p-values were obtained using Fisher's exact test. Thrombocytopenia was defined as a

platelet count below 150 × 10^9/L and reduced eGFR as below 60 mL/min/1.73 m^2. The exposure categories are not mutually exclusive. Bold p-values indicate statistical significance at $p<0.05$.

Multivariable Analysis of Pulmonary Complications

In separate logistic regression models adjusted for age and ISS, retinal microvascular abnormalities were associated with pulmonary complications (adjusted OR [aOR] 7.18; 95% CI 1.86–27.68; p=0.004), as did thrombocytopenia (aOR 3.97; 95% CI 1.39–11.36; p=0.010). The association for reduced eGFR was less precise and did not reach statistical significance after adjustment (aOR 3.16; 95% CI 0.90–11.04; p=0.071).

In the multivariable model including the three systemic abnormalities, age, and injury severity, retinal microvascular abnormalities remained associated with pulmonary complications (aOR 5.27; 95% CI 1.25–22.24; p=0.024), and thrombocytopenia also remained associated with the outcome (aOR 3.39; 95% CI 1.12–10.28; p=0.031). Reduced eGFR was associated with an elevated point estimate, although the confidence interval included the null value (aOR 2.51; 95% CI 0.65–9.69; p=0.183). Injury severity remained independently associated with pulmonary complications, with an aOR of 2.13 per five-point increase in ISS (95% CI 1.41–3.20; p<0.001). The regression estimates are summarized in Table 3.

Table 3. Exploratory multivariable logistic regression analysis of pulmonary complications

Predictor	Adjusted OR	95% CI	p-value
Retinal microvascular abnormalities	5.27	1.25–22.24	**0.024**
Thrombocytopenia	3.39	1.12–10.28	**0.031**
Reduced baseline eGFR	2.51	0.65–9.69	0.183
Age, per 10-year increase	1.53	0.96–2.42	0.073
ISS, per five-point increase	2.13	1.41–3.20	**<0.001**

OR, odds ratio; CI, confidence interval; ISS, Injury Severity Score; eGFR, estimated glomerular filtration rate. Estimates were obtained from a single exploratory multivariable logistic regression model containing all five predictors (n=120; 28 pulmonary events). The wide confidence intervals reflect the limited number of outcome events and should be considered when interpreting the adjusted estimates. Bold p-values indicate statistical significance.

Cumulative Systemic Abnormalities and Pulmonary Morbidity

The frequency of pulmonary complications increased with the number of concurrent baseline abnormalities. Among 70 patients without retinal microvascular changes, thrombocytopenia, or reduced eGFR, six (8.6%) developed pulmonary complications. The same happened with the corresponding frequency, which rose to 13 of 37 patients (35.1%) with one abnormality and nine of 13 patients (69.2%) with at least two abnormalities. The frequency of pulmonary complications rose with the systemic abnormality grades. Concurrently, retinal, hematological, and renal abnormalities were seen, with the observed gradient suggesting that this could be clinically informative, although the number in this group was small, making precision difficult.

Spectrum of Pulmonary Complications and Clinical Outcomes

Of those 28 patients who had pulmonary complications, the most common first qualifying event was pneumonia (11 patients; 39.3%), followed by acute respiratory distress syndrome (8 patients; 28.6%), otherwise unclassified hypoxemic respiratory failure (5 patients; 17.9%), and pulmonary thromboembolism (4 patients; 14.3%). The frequencies for the total population were 9.2%, 6.7%, 4.2%, and 3.3%, respectively.

Patients with pulmonary complications were more likely to have critical-care management. Of 28 patients with pulmonary complications, 16 (57.1%) needed intensive care compared with 6 of 92 (6.5%) without pulmonary complications. Pulmonary complication median length of stay was 13 days (IQR 10-17), versus eight days (IQR 6-11), for patients who did not develop pulmonary complications.

Medico-Legal Assessment

The medico-legal documentation emphasised the following: sequence of the primary skeletal injury, early systemic abnormalities, late pulmonary abnormalities, and the treatment

needs. More clinical morbidity (number of injuries, critical care admission, and hospital stay) was observed in patients who developed pulmonary complications. The chronological review provided information on the main orthopedic injuries and subsequent systemic complications and gave insights into the nature of the orthopedic injury-related morbidity. Objective data on the assessment of clinical progression were provided by retinal findings, hematological measurements, renal parameters, and respiratory investigations. These findings helped to establish the medical chronology and did not, per se, establish causal effect or medicolegal responsibility.

DISCUSSION

The present prospective cohort study showed that early changes in the retina and thrombocytopenia were associated with lung complications following traumatic long bone fracture. Pulmonary complications occurred in 23.3% of patients, most of these being pneumonia and acute respiratory distress syndrome (ARDS). The adjusted effect estimate was greatest for retinal abnormalities, followed by the adjusted effect estimate for thrombocytopenia, and the initial association with decreased baseline renal function was substantially less and no longer significant when fully adjusted. Furthermore, there was a significant increase in the rate of pulmonary complications with increasing systemic abnormalities. All these findings point towards the importance of multi-system assessment following skeletal trauma, as pulmonary derangement may occur through a variety of embolic, inflammatory, and endothelial mechanisms. In other studies, the wide spectrum of clinical signs and systemic manifestations of fat embolism and of major orthopedic trauma have been emphasized[1-3].

Retinal microvascular abnormalities were present in 12.5% of patients and associated with the presence of pulmonary complications at a higher rate (pulmonary complication 60.0% vs. 18.1%). This association was still present in the multivariable analysis (adjusted odds ratio [aOR] 5.27; 95% confidence interval [CI] 1.25 – 22.24)[4]. Retinal changes such as Cotton-Wool Spots, Intraretinal Hemorrhage, and Purtscher Type White Out can occur and are seen as capillary perfusion disturbances and associated with microembolization, endothelial injury, and systemic inflammation. Miguel et al. have identified trauma as an important underlying cause in the case of Purtscher's and Purtscher-like retinopathies (PLRs), and Serhan et al. have described the clinical features and systemic conditions associated with Purtscher's retinopathy. We believe that early retinal evaluation can be used in conjunction with evaluation of systemic injury after major skeletal trauma. In larger numbers of patients, the incremental value of these lesions to be used as a prognostic indicator should be assessed, and they are not pathognomonic of pulmonary fat embolism[3-5].

Thrombocytopenia was still associated with pulmonary complications, after adjustment for the other model covariates (aOR 3.39; 95% CI 1.12–10.28). Anomalies of platelet function after significant trauma could be due to bleeding and consumption, hemodilution, and inflammatory activation and interaction with damaged vascular endothelium. Platelets also participate in immune regulatory and microvascular inflammatory response[6]. Critically injured trauma patients were found to have an association between thrombocytopenia and organ dysfunction and requirement for organ support, with differing organ associations as determined by Rossetto et al. These observations are the ones that we are using in our analysis, which we are applying to adult patients with long bone fractures following trauma. In contrast, however, there was no statistically significant unadjusted association with anemia, suggesting that perhaps platelet abnormalities may be more valuable in this cohort as a contribution to information on pulmonary morbidity rather than reduced hemoglobin concentration alone[7-10].

A higher number of patients had pulmonary complications when their baseline renal function was impaired, and 15.0% of patients had impaired baseline renal function. Multivariable adjustment did not support the association (aOR 2.51, 95% CI 0.65 – 9.69), and the wide CIs suggested significant uncertainty about the size of the association. Biological pathways involved in renal and pulmonary dysfunction include increased inflammatory mediators, endothelial activation, fluid balance disorders, and microvascular regulation disorders[11]. A description of these mechanisms was given by Sullivan et al. in the form of lung–kidney crosstalk in critical illness. However, other factors, hemodynamics and hydration status, might affect the early assessment of renal function based on creatinine. Thus, a single eGFR value should not be used as a definite independent predictive

factor but rather in the overall clinical setting [6,12].

There was a gradual increase in baseline systemic abnormalities with increasing numbers of pulmonary complications. Respiratory complications occurred in 8.6%, 35.1% and 69.2% of patients with no, one and two or more abnormalities respectively[13]. This gradient suggests that perhaps patients with more profound systemic physiological injury are better represented by the simultaneous retinal, haematological and renal abnormalities. There was a strong association with pulmonary morbidity, as well, with the severity of injury, therefore underscoring the importance of correlating the anatomic findings of trauma with the laboratory and clinical findings. This is a small subgroup of individuals with 2 or more abnormalities; caution should be used in interpreting the size of the gradient – this is exploratory. Further research is needed to find out whether a combined assessment would be of measurable value to trauma severity measures that are already known[1,14].

The results also have significant medico-legal implications. Pulmonary complications were found to be associated with a significantly increased intensive care utilization and hospital length of stay, indicating that the consequences of a traumatic fracture may not be musculoskeletal. Good documentation of the circumstances of the injury, type of fracture, any systemic abnormalities at the time of the injury and after injury is important[15-18]. Objective evidence (ophthalmological examinations, haematological investigations and renal measurements and respiratory imaging) can serve as supporting evidence to the clinical record. Together, all of these records can help piece together the facts of the trauma and what it might have led to, and can help list a timeline of morbidity following the trauma. But a link does not prove causation or the possibility of prevention, and therefore, no liability to the person [7].

The strongest aspect of the study is its prospective cohort design, which used the same initial assessment and allowed a temporal gap between systemic abnormalities and eventual pulmonary outcomes. It has some methodological restrictions in interpreting the results. The precision of the adjusted estimates of the effects was limited by small sample sizes and few pulmonary events, especially retinal and renal abnormalities[19]. The associations observed may have been due to unmeasured confounding variables including hemorrhage, resuscitation, surgical management, and other comorbidities. Moreover, the composite pulmonary outcome included several items with underlying different pathophysiological mechanisms, and the 7-day period of observation might not have captured late pulmonary complications. Cumulative marker analysis was not validated externally, and the usage of this analysis in the clinic is yet to be assessed. Additional prospective, large-scale studies, including serial retinal imaging, hematological measures, renal function tests, and longer follow-up are warranted to validate the findings and to see if these relationships are reproducible and can be used for prognosis[8,20].

CONCLUSION

Early retinal microvascular abnormalities and thrombocytopenia remained associated with pulmonary complications after multivariable adjustment in adults with traumatic long-bone fractures. This correlation with lower baseline renal function was not significant after controlling for other variables. The more systemic abnormalities that were present, the more frequent the pulmonary complications were. These findings highlight the importance of examining retinal, haematological and renal parameters in addition to the existing trauma severity parameters. These findings might help identify patients with a high risk of respiratory morbidity after trauma and will help objectively document post-traumatic respiratory complications for medicolegal assessment. Multicentre cohorts are required to confirm their incremental prognostic value and possible clinical use for risk stratification purposes, particularly larger ones.

Competing Interests
The authors declare that they have no competing interests.

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Authors' Contributions
M.S.: Conceptualization, study design, methodology, and manuscript drafting. H.M.T.W.: Clinical assessment, investigation, and interpretation of findings. M.Y.K.: Medico-legal evaluation, data analysis, and critical manuscript revision. S.R.C.: Orthopedic assessment, data collection, and interpretation of results. S.R.: Data curation, statistical analysis, and manuscript editing. All authors reviewed and approved the final manuscript and agreed to be accountable for their respective contributions.

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