

Original Article

Incidence and related factors of hypoxia associated with elderly femoral neck fractures in the emergency department setting

Takashi Hongo,^{1,2} Hiromichi Naito,² Toshifumi Fujiwara,¹ Mototaka Inaba,² Noritomo Fujisaki,² and Atsunori Nakao²

¹Emergency Department, Okayama Saiseikai General Hospital, and ²Department of Emergency, Critical Care, and Disaster Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

Aim: Femoral neck fractures in elderly patients needing oxygen therapy are often encountered in the emergency department. This single-center, retrospective, observational study aimed to examine the frequency, cause, and factors related to hypoxia in elderly patients with femoral neck fractures.

Methods: We analyzed data from 241 patients admitted to Okayama Saiseikai General Hospital (Okayama, Japan) from April 2016 to March 2019. Hypoxia was defined as PaO₂ / FiO₂ ratio under 300. The independent factors for hypoxia were determined by multiple logistic regression analysis.

Results: There were 194 patients who met the study inclusion criteria, 148 in the non-hypoxia group and 46 in the hypoxia group. The hypoxia group included patients with pneumonia ($n = 3$), chronic obstructive pulmonary disease ($n = 2$), pulmonary edema ($n = 1$), and pulmonary embolization ($n = 1$). The cause of hypoxia was undetermined in 39 cases. However, occult fat embolism syndrome was suspected in 29 of these 39 cases based on Gurd and Wilson criteria after considering clinical examination results. Barthel indexes were significantly lower in the hypoxia group on discharge. Age (adjusted odds ratio [OR] 1.07; 95% confidence interval [CI], 1.00–1.14; $P = 0.038$), D-dimer (adjusted OR 1.02; 95% CI, 1.00–1.03; $P = 0.005$), and transtricuspid pressure gradient (adjusted OR 1.03; 95% CI, 1.00–1.07; $P = 0.015$) were independently associated with the hypoxia.

Conclusion: We found that hypoxia, including undetermined hypoxia, was commonly encountered in the emergency department. Hypoxia in elderly patients with femoral neck fractures was associated with age, D-dimer, and transtricuspid pressure gradient and needs further investigation.

Key words: D-dimer, geriatric, hypoxia, injury, TRPG

INTRODUCTION

THE NUMBER OF patients with osteoporosis and fragility-related fractures has increased in most developed countries.¹ Femoral neck fractures associated with fragility increases societal burdens in terms of mortality and quality of life in the elderly population, as well as economic costs.¹

Corresponding: Hiromichi Naito, MD PhD, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Department of Emergency, Critical Care, and Disaster Medicine, 2-5-1 Shikata, Kita-ku, Okayama, Japan 700-8558. E-mail: naito.hiromichi@okayama-u.ac.jp

Received 22 Aug, 2020; accepted 29 Nov, 2020

Funding Information

This study was partially supported by the Japan Society for the Promotion of Science KAKENHI (grant number JP 18K08887).

Recently, early surgery for femoral neck fracture was recommended to reduce complications, improve morbidity, and shorten hospital stay.² Patient-specific factors such as age, male gender, and general health status, comorbidities, and postoperative complications influence high morbidity and long hospitalization.³ Hypoxia during the postoperative period is also associated with higher morbidity and mortality due to complications.⁴ However, preoperative hypoxia associated with femoral neck fractures in the emergency department has not fully been investigated. Therefore, this study aimed to investigate the frequency, etiology, characteristics, related factors, and outcomes of the early hypoxia seen in the elderly patients with femoral neck fractures in the emergency department setting. The results of this study could help emergency physicians understand the association between fragility fracture and hypoxia in the increasing elderly population.

METHODS

THE STUDY WAS approved by a suitably constituted ethics committee of our institution (Committee of Okayama Saiseikai General Hospital, ID: 200101). Patient consent was waived. The study conforms to the provisions of the Declaration of Helsinki.

Study design and population

This single-center, retrospective, observational study was carried out using the electronic medical records of patients with femoral neck fractures who were admitted to the emergency department of Okayama Saiseikai General Hospital (Okayama, Japan) during the 3-year period from April 2016 to March 2019. The study included patients admitted to our hospital after diagnosis of femoral neck fractures confirmed with computed tomography (CT) in the emergency department. Patients under 60 years old and patients with insufficient arterial gas analysis were excluded.

Patient grouping and hypoxia diagnostic process

Hypoxia was defined as a $\text{PaO}_2 / \text{FiO}_2$ (P/F) ratio ≤ 300 mmHg based on the previous studies,⁵ then patients were divided into hypoxia and non-hypoxia groups. After general physical examinations, causes of hypoxia in all patients in the hypoxia group were investigated using laboratory test results, chest X-rays, chest CT images, and/or echocardiography. Lung-related diseases such as pneumonia, chronic obstructive pulmonary disease, pulmonary embolization, and pulmonary edema due to heart failure were diagnosed based on chest CT images and X-rays with alveolar consolidation, interstitial infiltrates, or interstitial edema. Test results such as high serum C-reactive protein, B-type natriuretic peptide, and/or D-dimer were evaluated. Other tests like sputum culture or echocardiography were carried out when needed.^{6,7,8} The attending physician, emergency physician, and/or internal physician comprehensively diagnosed the cause of hypoxia. Hypoxia with unknown cause was defined as undetermined hypoxia after all examinations were carried out by the attending physician.

Outcomes

The primary outcome of the study was to identify the incidence and classify the causes of hypoxia in neck fracture patients in the emergency department. The secondary outcome was to determine the risk factors associated with hypoxia.

Data collection

We collected the following data from patients' medical records: laboratory values (white and red blood cell counts, platelet count, hemoglobin, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, albumin, total protein, total bilirubin, C-reactive protein, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, amylase, B-type natriuretic peptide, D-dimer, prothrombin time, activated partial thromboplastin time, and arterial blood gas), clinical data (age, sex, weight, height, walking ability, whether or not the patient was living in a residential facility, and injury mechanism), medical history (hypertension, diabetes, cerebrovascular disease, chronic kidney disease, congestive heart failure, cirrhosis, cancer, dementia, and fracture), home oxygen therapy, region of fracture, vital signs, the presence of petechiae, Garden classification, use of echocardiography and contrast CT, duration of oxygen administration excluding the perioperative period, time to surgery, use of mechanical ventilation, vasopressor administration, Barthel index on admission and discharge, and length of hospital stay. Transthoracic echocardiography was undertaken to measure the transtricuspid pressure gradient (TRPG) derived from peak transtricuspid jet velocity by cardiologists, well-trained attending emergency physicians, and certified ultrasonography technicians.

Statistical analysis

Categorical data were expressed as proportions and continuous data were expressed as median and interquartile range values. The Mann–Whitney *U*-test was used to compare continuous variables; Fisher's exact probability test was used to compare categorical variables. A multivariable logistic regression model was used to examine the dependent variable associated with hypoxia (age, Garden classification [3 or 4], white blood cell [WBC] count, D-dimer, TRPG). We calculated odds ratios (ORs) derived from the logistic regression model.

SPSS version 15.0 (Chicago, IL, USA) was used for statistical analysis. *P*-values < 0.05 were considered statistically significant.

RESULTS

Incidence and etiology of hypoxia

DURING THE 3-year study period, 241 patients were admitted to our hospital's emergency department for femoral neck fractures. After excluding cases with insufficient arterial gas analysis ($n = 42$) and those under 60 years

old ($n = 5$), 194 cases met the inclusion criteria. **Figure 1** shows our study design flow chart. Forty-six (46) of those elderly patients with neck fractures had hypoxia (23.8%, hypoxia group). One hundred and forty-eight (148) patients did not have hypoxia (76.2%, non-hypoxia group). Etiologies of the hypoxia group included pneumonia (three cases, 6.5%), chronic obstructive pulmonary disease (two cases, 4.3%), pulmonary edema (one case, 2.1%), and pulmonary embolization (one case, 2.1%). The etiology of hypoxia in 39 cases (84.7%) remained undetermined. According to Gurd and Wilson criteria (**Table 1**), 29 of 39 cases (74.4%) matched to the criteria of fat embolism syndrome (FES).⁹

Baseline characteristics of hypoxia group

Table 2 shows the demographic and clinical characteristics of the study cohort. Patients in the hypoxia group were statistically older than those in the non-hypoxia group (88 versus 83 years old). Glasgow Coma Scale scores were lower in the hypoxia group (14 versus 15). Respiratory rate (20 versus 18 breaths/min), and heart rate (85 versus 79 b.p.m.) were higher in the hypoxia group. The number of patients with femoral fractures categorized as Garden 3 or 4 was 42/46 (91.3%) in the hypoxia group and 114/148 (77.0%) in non-hypoxia group, respectively. Medical history did not differ between the groups. The P/F ratios of the hypoxia group and the non-hypoxia group were 258 and 363, respectively. The WBC count (10650 versus 8620/ μL), D-dimer level (39.6 versus 16.7 $\mu\text{g/mL}$), and TRPG (34 versus 20 mmHg) were significantly higher in patients with hypoxia than in the non-hypoxia patients. Frequency of surgery did not differ between the groups (42/46 [91.3%] versus 143/148 [96.6%]). Time to surgery from admission was longer for hypoxic patients than for non-hypoxic patients (5 versus 4 days). The period of oxygen therapy was longer for

Table 1. Cause of hypoxia in elderly patients with femoral neck fractures in the emergency department ($n = 46$)

	Hypoxia group ($n = 46$)
Cause	
Pneumonia	3/46 (6.5)
COPD	2/46 (4.3)
Pulmonary edema	1/46 (2.1)
PE	1/46 (2.1)
Undetermined	39/46 (84.7)
Occult FES	29/39 (74.4)
Other	10/39 (25.6)

Data are shown as number (%).

COPD, chronic obstructive pulmonary disease; FES, fat embolism syndrome; PE, pulmonary embolism.

the hypoxia cases than for the non-hypoxic cases (4 versus 0 days). No patient required mechanical ventilation or vasopressor use. Barthel index scores at discharge were significantly lower in the hypoxia group (40 versus 60), although it was not different on admission (5 versus 10). Hospital length of stay did not differ between the groups (24 versus 26 days).

Risk factors associated with hypoxia

In the univariable logistic regression analysis, older age, Garden classification (3 or 4), higher WBC value, higher D-dimer value, and higher TRPG value were risk factors associated with hypoxia. In the multivariable analysis, age (adjusted OR 1.07; 95% confidence interval [CI], 1.00–1.14; $P = 0.038$) D-dimer (adjusted OR 1.02; 95% CI, 1.00–1.03; $P = 0.005$), and TRPG (adjusted OR 1.03; 95% CI, 1.00–1.07; $P = 0.015$) were independently associated with hypoxia in patients with femoral neck fractures (**Table 3**).

DISCUSSION

ALTHOUGH PREVIOUS STUDIES have reported that many patients with femoral neck fractures are already hypoxemic on admission to hospital, the relationship between hypoxia and femoral neck fractures has not been fully elucidated.¹⁰ Our study determined the incidence of hypoxia among patients with femoral neck fractures in the emergency department was 23.8%, which was a much higher incidence than that found in a previous report by Jin *et al.* (13.8%).⁴ Our study also revealed that elevated age, D-dimer, and TRPG were independent factors related to hypoxia in multivariate analysis and might suggest the possibility of additional multiple pathologies, including

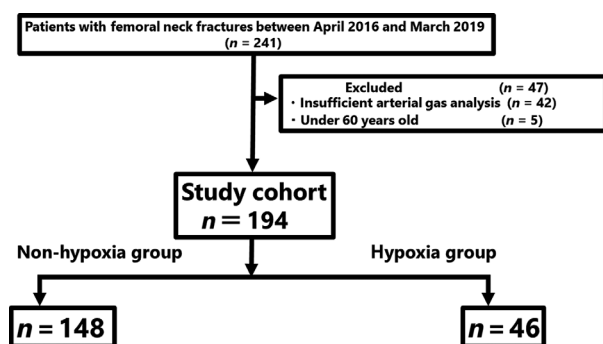


Fig. 1. Study design flow chart. The incidence of hypoxia and non-hypoxia in elderly neck fracture patients was 46/194 (23.8%) and 148/194 (76.2%), respectively.

Table 2. Characteristics of elderly patients treated for femoral neck fractures ($n = 194$)

	Non-hypoxia group ($n = 148$)	Hypoxia group ($n = 46$)	P-value
Patient characteristics			
Male gender	38/148 (23.0)	6/46 (13.0)	0.105
Age, years	83 (75–87)	88 (85–91)	<0.001*
Height, cm	153 (148–158)	150 (145–155)	0.005*
Weight, kg	46.9 (40.7–52.5)	47.3 (43.3–53.7)	0.303
Region (right)	72/148 (48.2)	26/46 (56.5)	0.400
Garden classification (1 or 2)	34/148 (23.0)	4/46 (8.7)	0.034*
Garden 1	8/148 (5.4)	0/46 (0.0)	0.202
Garden 2	26/148 (17.5)	4/46 (8.6)	0.168
Garden classification (3 or 4)	114/148 (77.0)	42/46 (91.3)	0.034*
Garden 3	19/148 (12.8)	4/46 (8.6)	0.604
Garden 4	95/148 (64.1)	38/46 (82.6)	0.019*
Fall injury	148/148 (100.0)	46/46 (100.0)	1.000
Blood pressure, mmHg	155/83 (140–169/71–94)	147/85 (134–163/75–98)	0.504/0.132
Glasgow Coma Scale score	15 (14–15)	14 (14–14)	0.003*
Respiratory rate, breaths/min	18 (16–20)	20 (18–24)	0.002*
Temperature, °C	36.8 (36.4–37.3)	37.0 (36.7–37.5)	0.053
Heart rate, b.p.m.	79 (70–89)	85 (75–98)	0.018*
Walking ability	137/148 (92.3)	44/46 (95.6)	0.737
Residential facilities	58/148 (39.8)	25/46 (54.3)	0.088
Hypertension	103/148 (69.9)	37/46 (80.4)	0.188
Diabetes	32/148 (21.6)	10/46 (21.7)	1.000
Cirrhosis	7/148 (4.8)	5/46 (10.8)	0.160
CVD	28/148 (18.1)	7/46 (15.2)	0.665
CHF	39/148 (26.5)	9/46 (19.5)	0.436
Cancer	33/148 (20.2)	5/46 (10.8)	0.094
CKD	29/148 (18.8)	8/46 (17.3)	0.832
Dementia	62/148 (41.8)	24/46 (52.1)	0.238
Home oxygen therapy	0/148 (0.0)	2/46 (4.3)	0.055
History of fracture	25/148 (17.4)	7/46 (15.2)	0.737
Examination			
Total protein, g/dL	6.7 (6.2–7.1)	6.5 (6.3–6.8)	0.317
Albumin, g/dL	3.7 (3.3–4.0)	3.6 (3.3–3.9)	0.340
Red blood cells, $10^4/\mu\text{L}$	395 (349–424)	350 (330–393)	0.441
White blood cells, μL	8620 (7095–11 035)	10650 (9470–12 215)	0.004*
Hemoglobin, g/dL	11.2 (10.8–12.5)	10.9 (10.0–12.2)	0.214
Platelets, $10^4/\mu\text{L}$	18.5 (15.3–24.8)	15.7 (12.5–21.7)	0.196
C-reactive protein test, mg/dL	0.21 (0.06–2.39)	0.21 (0.05–2.51)	0.571
BUN, mg/dL	19.0 (13.5–23.9)	27.0 (14.0–24.9)	0.645
Serum creatinine, mg/dL	0.66 (0.53–0.89)	0.69 (0.55–0.97)	0.826
eGFR, mL/min	68.7 (55.2–87.7)	60.5 (40.2–85.4)	0.344
Total bilirubin, mg/dL	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.113
Alkaline phosphatase, U/L	242 (205–314)	236 (201–310)	0.859
Aspartate aminotransferase, U/L	24 (19–30)	20 (17–32)	0.150
Alanine aminotransferase, U/L	18 (14–23)	15 (13–19)	0.027*
Amylase, U/L	75 (54–97)	82 (61–119)	0.823
PT, %	100 (86–105)	91 (78–99)	0.070
APTT, sec	29.8 (27.9–32.2)	31.0 (29.8–32.3)	0.193
D-dimer, $\mu\text{g/mL}$	16.7 (7.7–38.7)	39.6 (21.3–102.5)	0.001*
P/F ratio	363 (340–401)	258 (212–280)	<0.001*

Table 2. (Continued)

	Non-hypoxia group (n = 148)	Hypoxia group (n = 46)	P-value
Lactate, mmol/L	1.1 (0.9–1.6)	1.1 (0.9–1.6)	0.361
BNP, pg/mL	56.7 (19.1–125.5)	61.3 (38.0–143.5)	0.457
Echocardiography	109/146 (80.1)	36/46 (78.2)	0.567
TRPG, mmHg	20 (4–26)	34 (25–39)	<0.001*
Contrast enhanced CT	4/146 (2.7)	21/46 (45.6)	<0.001*
Petechiae	0/148 (0)	0/46 (0)	N/A
Intervention			
Orthopedic surgery	143/148 (96.6)	42/46 (91.3)	0.220
Time to surgery, days	4 (2–5)	5 (4–7)	<0.001*
Period of oxygen therapy, days	0 (0–0)	4 (0–9)	<0.001*
Mechanical ventilation	0/147 (0)	0/46 (0)	N/A
Vasopressor administration	0/147 (0)	0/46 (0)	N/A
Outcome			
Barthel index score on admission	10 (5–15)	5 (0–10)	0.077
Barthel index score on discharge	60 (32–75)	40 (15–60)	0.004*
Hospital stay, days	26 (18–34)	24 (18–29)	0.143

Continuous variables are presented as median (interquartile range); categorical variables are shown as frequency (%).

APTT, activated partial thromboplastin time; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; CT, computed tomography; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; P/F, PaO₂ / FIO₂; PT, prothrombin time; TRPG, transtricuspid pressure gradient.

*P < 0.05 is considered statistically significant. P-values were calculated using Fisher's exact probability test or the Mann–Whitney U-test.

Table 3. Multiple logistic regression analysis of risk factors associated with hypoxia in elderly patients treated for femoral neck fractures

Risk factor	OR (95% CI)	P-value
Age	1.07 (1.00–1.14)	0.038
Garden classification (3 or 4)	3.82 (0.72–20.33)	0.115
WBC	1.00 (1.00–1.00)	0.249
D-dimer	1.02 (1.00–1.03)	0.005
TRPG	1.03 (1.00–1.07)	0.015

Age, Garden classification (3 or 4), white blood cell count (WBC), D-dimer, and transtricuspid pressure gradient (TRPG) were used to adjust for the outcomes in the multivariable logistic regression.

CI, confidence interval; OR, odds ratio.

anatomical and physiological changes by aging, post-traumatic pulmonary microthromboembolism, FES, and damage-associated molecular patterns. However, in 84.7% of hypoxic patients, the cause of hypoxia could not be fully determined in our study.

Aging can cause anatomical and physiological changes in the respiratory system. After age 75 years, arterial oxygen

tension gradually declines to 83 mmHg, approximately equivalent to a P/F ratio of 395.¹¹ In our study, the P/F ratio in the non-hypoxia group was close to the physiologically aged P/F (363 versus 395); moreover, the P/F of the hypoxia group was significantly lower than that of the normal population (258 versus 395; 192 of 194 patients did not need home oxygen therapy before administration). It seems that hypoxia cannot be fully explained only by deteriorated respiratory function due to aging.

Severe adult respiratory distress syndrome or mechanical obstruction of the pulmonary artery flow might be associated with D-dimer and TRPG.^{12,13} We undertook contrast enhanced CT for 17 of 39 cases with undetermined hypoxia, however, the cause of hypoxia could not be determined. Hypoxia improved without the use of anticoagulant therapy in all undetermined hypoxia cases regardless of the use of contrast enhanced CT, suggesting that pulmonary microembolization might not be the main cause in undetermined hypoxia cases.

Another possible pathology of hypoxia in patients with undetermined reason could be occult FES. According to two major Gurd and Wilson criteria (hypoxia and altered mentality), 29 of 39 cases were matched to FES diagnostic criteria (Table 1).⁹ In our study, the Glasgow Coma Scale score was 14 in 23 of 29 cases and it might be difficult to distinguish

the major criteria of FES from delirium or dementia in elderly populations. However, Lindeque *et al.* reported that FES can be diagnosed only on the basis of respiratory parameters.¹⁴ In fact, Aggarwal *et al.* described 10 of 10 patients who presented with hypoxia.¹⁵ Based on criteria established in the 1970s, FES is diagnosed by the exclusion of other diseases and the presence of characteristic signs and symptoms with an underlying cause without an objective standard parameter, including laboratory and/or imaging findings.¹⁵

Hypoxia with major trauma-induced acute respiratory distress syndrome or acute lung injury is a well-known concept.^{16,17} Damage-associated molecular patterns caused by fractures induce local and systemic inflammation with neutrophil activation and release of cytokines, leading to indirect lung injury in experimental animal models.^{16,18} Therefore, femoral neck fractures might induce lung damage and, subsequently, hypoxia.

Hypoxia in femoral neck fracture patients during the perioperative period might delay healing after the surgical repair, as it influences low Barthel indexes on discharge. Following bone fracture, bone and soft tissue are ruptured, damaging the blood vessels. Blood and bone marrow cells ingress and are disturbed from the nutrient and oxygen supply at the injury site.¹⁹ This process leads to hypoxia in the local tissue and an inflammatory reaction, which is a determining factor of fracture-healing outcomes.¹⁹ Hypoxia itself reduces the oxygen supply in local tissue.

This study has several limitations. First, it was a single-center, retrospective, observational design with a small number of patients with femoral neck fractures included in the analysis. Second, this study was undertaken in a single medical institution, so there were issues with expenses and requests for laboratory tests and images, depending on the treating physicians. Additionally, arterial gas analysis, echography, and contrast enhanced CT were based on the preference of the attending physician. Finally, we were unable to access medical records following patient discharge. Further multicenter studies with a prospective design could be needed to unravel further pathologies for hypoxia, as elderly populations are at increased risk for fragility fractures.

CONCLUSION

IN THIS RETROSPECTIVE analysis, we found that hypoxia with femoral neck fracture was commonly encountered in elderly patients in the emergency department. Elderly hypoxic patients with femoral neck fractures were associated with increased age, D-dimer level, and

TRPG. Elevated levels of D-dimer and TRPG might suggest additional pathologies, which could need further evaluation as potential causes of hypoxia in elderly patients with neck fractures in the emergency department.

ACKNOWLEDGMENTS

THIS STUDY WAS partially supported by JSPS KAKENHI (grant number JP 18K08887). The authors thank Christine Burr for editing the manuscript.

DISCLOSURE

Approval of research protocol: The study was approved by the ethics committee of our institution (Committee of Okayama Saiseikai General Hospital, ID: 200101).

Informed consent: Informed consent was waived.

Registration and registration no. of the study/trial: Registration no. 200101.

Animal studies: N/A.

Conflict of interest: None.

REFERENCES

- 1 Johnell OKJ. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos. Int.* 2006; 17: 1726–33.
- 2 Smektala R, Endres HG, Dasch B, *et al.* The effect of time-to-surgery on outcome in elderly patients with proximal femoral fractures. *BMC Musculoskelet Disord.* 2008; 9: 1–9.
- 3 Flikweert ER, Wendt KW, Diercks RL, *et al.* Complications after hip fracture surgery: are they preventable? *Eur. J. Trauma Emerg. Surg.* 2018; 44: 573–80.
- 4 Jin J, Wang G, Gong M, Zhang H, Liu J. Retrospective comparison of the effects of epidural anesthesia versus peripheral nerve block on postoperative outcomes in elderly chinese patients with femoral neck fractures. *Clin. Interv. Aging.* 2015; 10: 1223–31.
- 5 Roupie E, Lepage E, Wysocki M, *et al.* Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. *Intensive Care Med.* 1999; 25: 920–9.
- 6 Mandell LA. Community-acquired pneumonia: an overview. *Postgrad. Med.* 2015; 127: 607–15.
- 7 Long B, Koyfman A, Gottlieb M. Diagnosis of acute heart failure in the emergency department: an evidence-based review. *West J. Emerg. Med.* 2019; 20: 875–84.
- 8 Yang S, Wang J, Kuang T, *et al.* Efficacy and safety of bronchial artery embolization on hemoptysis in chronic thromboembolic pulmonary hypertension: a pilot prospective cohort study. *Crit. Care Med.* 2019; 47: e182–e189.

- 9 Gurd AR. Fat embolism: an aid to diagnosis. *Bone Jt Surg. Br.* 1970; 52: 732–7.
- 10 Martin VC. Hypoxaemia in elderly patients suffering from fractured neck of femur. *Anaesthesia* 1977; 32: 852–67.
- 11 Alvis BD, Hughes CG. Physiology considerations in the geriatric patient. *Anesth. Clin.* 2015; 33: 447–56.
- 12 Brotfain E, Koyfman L, Kutz R, *et al.* Use of early inhaled nitric oxide therapy in fat embolism syndrome to prevent right heart failure. *Case Reports Crit. Care.* 2014; 2014: 1–4.
- 13 Shah TG, Wadia SK, Kovach J, Fogg L, Tandon R. Echocardiographic parameters of right ventricular function predict mortality in acute respiratory distress syndrome: A pilot study. *Pulm. Circ.* 2016; 6: 155–60.
- 14 Lindeque BG, Schoeman HS, Dommissie GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. *J. Bone Jt Surg. Br.* 1987; 69: 128–31.
- 15 Aggarwal R, Banerjee A, Soni KD, Kumar A, Trikha A. Clinical characteristics and management of patients with fat embolism syndrome in level I Apex Trauma Centre. *Chinese J. Traumatol.* 2019; 22: 172–6.
- 16 Balogh ZJ, Reumann MK, Gruen RL, *et al.* Advances and future directions for management of trauma patients with musculoskeletal injuries. *Lancet* 2012; 380: 1109–19.
- 17 Tignanelli CJ, Hemmila MR, Rogers MAM, Raghavendran K. Nationwide cohort study of independent risk factors for acute respiratory distress syndrome after trauma. *Trauma Surg. Acute Care Open* 2019; 4: 1–9.
- 18 Kurt A, Turut H, Acipayam A, *et al.* Investigation of surfactant protein-D and interleukin-6 levels in patients with blunt chest trauma with multiple rib fractures and pulmonary contusions: A cross-sectional study in Black Sea Region of Turkey. *BMJ Open.* 2016; 6: 1–8.
- 19 Kolar P, Gaber T, Perka C, Duda GN, Buttgerit F. Human early fracture hematoma is characterized by inflammation and hypoxia. *Clin. Orthop. Relat. Res.* 2011; 469: 3118–26.