Original Article

Loss of bone mineral density following sepsis using Hounsfield units by computed tomography

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Aim: To examine the change in vertebral bone mineral density (BMD) using abdominal computed tomography in patients treated for sepsis.

Methods: A single-center, retrospective, observational study was undertaken to evaluate BMD after critical care at Okayama Saiseikai General Hospital (Okayama, Japan) from January 2016 to April 2018. Sepsis was defined as an absolute increase of ≥2 in Sequential Organ Failure Assessment score in the intensive care unit or high care unit. Bone mineral density was evaluated in Hounsfield units (HU) by computed tomography. Patients were divided into groups based on the presence or absence of osteoporosis, which was defined as average vertebral body HU <110. Paired *t*-tests were used to compare the mean BMD of each vertebra between before and after critical care. We also analyzed accidental bone fracture events after discharge. The survival rate was analyzed as an outcome using the Kaplan–Meier method.

Results: Fifty-two of 188 patients met the inclusion criteria. We found significant differences between admission and follow-up vertebral BMD values in the spine at the thoracic 12, lumbar 1–5, and sacrum 1 levels ($P < 0.05$), especially in the non-osteoporosis groups. No difference in mortality was observed between patients with osteoporosis and those without. Two of 19 patients with osteoporosis developed a bone fracture.

Conclusion: We found that sepsis was associated with loss in BMD following critical care.

Key words: Bone mineral density, computed tomography, critical care, osteoporosis, sepsis

INTRODUCTION

ADVANCES IN CRITICAL care medicine have resulted in the growing population of survivors of critical illness. Many survivors experience impairment in cognition, mental health, and physical function, known as postintensive care syndrome.[1] Osteoporosis, which is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility, results in decreased bone strength and increased risk of fracture. It is a major threat to quality of life.[2] Some studies have reported an association between critical illness and accelerated bone turnover, an increase in bone turnover markers during critical illness, accelerated loss of bone mineral density (BMD) in the year following critical illness, and increased fragility fractures in survivors of critical illness.[3] However, there has been little focus on bone loss during critical care.

Sepsis results in systemic inflammatory response syndrome, which induces inflammatory cytokine production. These cytokines induce osteoclastogenesis and bone resorption, with calcium mobilization into the circulation from bone stores.[4]

Osteoporosis is a major public health concern. A clinical diagnosis of osteoporosis can be made in the presence of a fragility fracture, particularly at the spine, hip, wrist, humerus, rib, and pelvis, or with a *T*-score ≤ -2.5 standard deviation at any site based on BMD measurement by dual-energy X-ray absorptiometry (DXA).[5] In the absence of a fragility fracture, BMD assessment by DXA is the standard test to diagnose osteoporosis, according to the classification of the World Health Organization.[5] In the emergency department, it is difficult to evaluate BMD in patients who are

hemodynamically unstable or when the DXA is difficult to access. According to some published reports, computed tomography (CT) densitometry is equal or superior to DXA for assessing vertebral fracture risk.[6] Computed tomography attenuation numbers or values, measured in Hounsfield units (HU), can be attained prospectively or retrospectively from all clinical CT studies and can be used to estimate BMD without added costs or radiation.[6] However, there are few reports on the assessment of BMD change during sepsis using CT.

The aim of this study is to examine changes in BMD between admission and after critical care based on spine HU in patients with sepsis.

METHODS

THE PROTOCOL FOR this study was approved by a suitably constituted ethics committee of the institution (Committee of Okayama Saiseikai General Hospital), and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all patients or surrogate decision-makers for study inclusion.

This retrospective study was carried out using electronic medical records of patients admitted for sepsis or septic shock to the intensive care unit (ICU) or high care unit (HCU) of Okayama Saiseikai General Hospital (Okayama, Japan) from January 2016 to April 2018. Sepsis and septic shock were defined according to the Sepsis-3 criteria.[7] Patients with suspected or documented infection and an acute increase in Sequential Organ Failure Assessment (SOFA) score of ≥2 points on admission were included. Septic shock can be clinically identified based on vasopressor requirement to maintain a mean arterial pressure of ≥65 mmHg and serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.[7] The study included patients who underwent abdominal CT on admission and follow-up CT. The attending physicians determined the strategy for sepsis treatment and the timing of follow-up CT for each patient. The study exclusion criteria were discharge within 1 week from admission, admission to the general wards, or insufficient clinical data.

We used an 80 detector row CT scanner (Aquilion Prime; Toshiba Medical Systems, Totigi, Japan). Scanning parameters were as follows: tube voltage, 120 kVp; CT auto exposure control maximum, 550 mA; nose index, 10; gantry rotation time, 0.5 s; beam pitch; and detector collimations, 0.5 mm. The CT images were reconstructed in the axial plane (section thickness, 0.5 mm) at 0.3 mm intervals using the ADIR algorithm (Canon Medical, Totigi, Japan) with FC13 kernel. The method of BMD assessment using CT attenuation was to obtain axial and sagittal planes (Fig. 1).

Computed tomography attenuation was measured by locating the midvertebral body in the sagittal plane. Computed tomography attenuation was measured in HU by placing a click-and-drag elliptical region of interest (ROI) within axial sections of vertebral trabecular bone, avoiding the vertebrobasilar complex, mild degenerative changes, and cortical surfaces. The CT software reported the average CT attenuation of the ROI in HU. These methods have been evaluated and shown to produce reliable results.[6,8] We measured thoracic vertebra (Th) 12, lumbar vertebrae (L) 1–5, and sacrum vertebra (S) 1. We calculated HU on admission and at the first follow-up CT after admission.

Patients were divided into groups based on the presence or absence of osteoporosis, which was defined as average vertebral body HU <110 (90% specificity), as described by Young *et al.*[9], on admission.

We collected the following data from the medical record: white blood cell count, C-reactive protein, calcium, arterial blood gas values, clinical information (age, sex, use of tobacco, and alcohol), medical history (diabetes, hypertension, cerebrovascular disease, congestive heart failure, chronic kidney disease, and malignancy), previous use of osteoporosis drugs, vital signs and SOFA on admission, Acute Physiology and Chronic Health Evaluation II in the ICU/HCU, and accidental bone fracture after discharge.

Continuous variables are presented as median and interquartile ranges, and categorical variables are reported as frequencies or percentages. Parametric and non-parametric methods (*t*-test or Mann–Whitney test, respectively) were used as appropriate after establishing normality of distribution by the Kolmogorov–Smirnov or Shapiro–Wilk test. Categorical variables were compared using Fisher's exact probability test. Paired *t*-tests were used to compare the mean HU of each vertebra in groups before and after critical care.

The survival times were calculated using the Kaplan–Meier method, and comparisons between groups were made with the log-rank test. *P*-values <0.05 were considered statistically significant. All statistical analyses were undertaken using EZR version 1.11 (Jichi Medical University, Shimotsukeshi, Japan).

RESULTS

DURING THE 3-year study period, a total of 188 patients were admitted to the emergency department of our hospital for sepsis or septic shock. Of these patients, 52 met the inclusion criteria. Figure 2 shows the derivation of the study population and workup for osteoporosis. Nineteen patients had osteoporosis on admission. The demographic and clinical characteristics of the study cohort are shown in
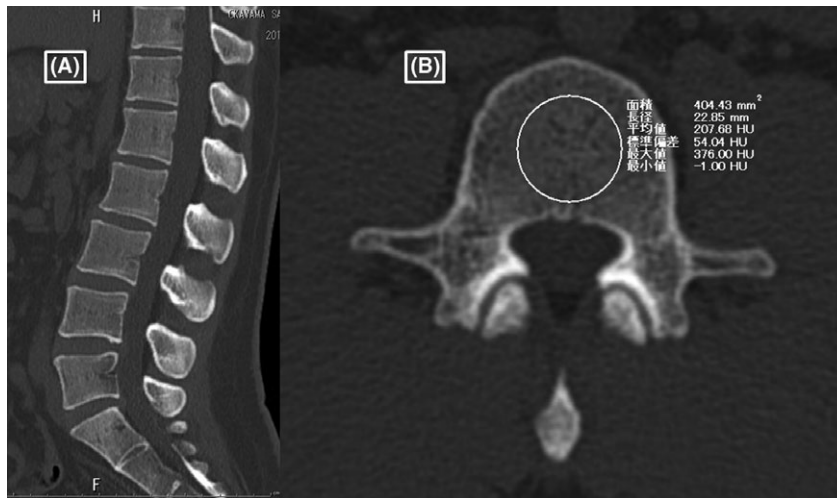
Fig. 1. Bone mineral density was evaluated in Hounsfield units (HU) by computed tomography (CT). A, CT attenuation was measured by first locating the midvertebral body in the sagittal plane. B, CT attenuation was measured in HU by placing a click-and-drag elliptical region of interest within axial sections of the vertebral trabecular bone, avoiding the vertebrobasilar complex, mild degenerative changes, and cortical surfaces. The CT software reported the average CT attenuation of the region of interest in HU.
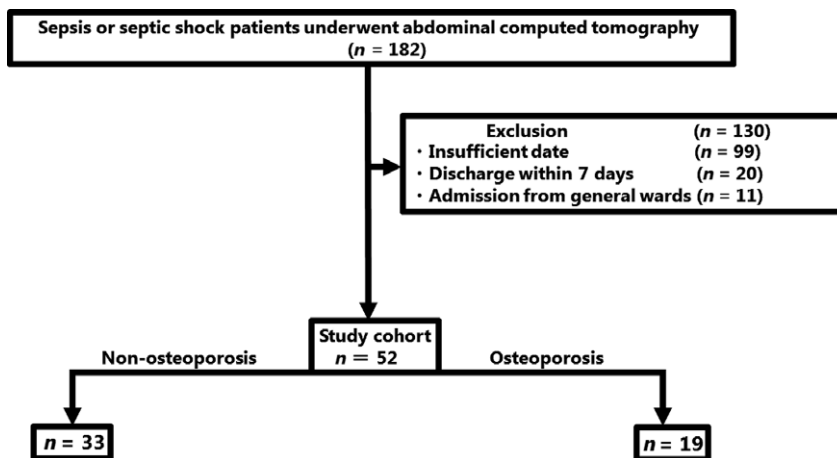
Fig. 2. Flowcharts of patients with osteoporosis or without osteoporosis. Fifty-two patients met the inclusion criteria.

Table 1. There was no significant difference between the osteoporosis and non-osteoporosis groups on admission except age.

Figures 3 and 4 show a plot of HU values according to ROIs on admission CT and follow-up CT. We found significant differences between admission and follow-up CT vertebral bone HU at the Th12 ($P = 0.005$), L1 ($P = 0.014$), L2 ($P = 0.009$), L3 ($P < 0.001$), L4 ($P < 0.001$), L5 ($P = 0.001$), and S1 ($P < 0.001$) levels (Fig. 3). In the non-osteoporosis group, there were significant HU decreases at the Th12 ($P < 0.001$), L1 ($P < 0.001$), L2 ($P < 0.001$), L3 ($P < 0.001$), L4 ($P < 0.001$), L5 ($P < 0.001$), and S1 ($P < 0.001$) levels (Fig. 4A). Seven of 33 non-osteoporosis

patients became osteoporotic based on HU. In contrast, there was a significant HU decrease only at the S1 ($P < 0.001$) level (Fig. 4B) in the osteoporotic group. Two of 52 patients developed a bone fracture, both in the osteoporosis group. One patient developed a femoral neck fracture, and one patient developed a lumbar compression fracture.

Figure 5 shows the 90-day outcomes of the two groups. No mortality difference was found between groups.

DISCUSSION

TO THE BEST of our knowledge, this is the first study to investigate changes in BMD due to critical care

Table 1. Characteristics of patients who were treated for sepsis or septic shock and underwent abdominal computed tomography (n = 52)

	Non-osteoporosis (*n* = 33)	Osteoporosis (*n* = 19)	*P*-value
Male gender, *n*	9/33	7/19	0.534
Age, years	73 (67–83)†	84 (75–87)†	0.027
Systolic blood pressure, mmHg	90 (79–116)†	88 (78–117)	0.961
Diastolic blood pressure, mmHg	58 (49–65)†	53 (42–72)	0.567
Glasgow Coma Scale	14 (7–15)†	14 (12–14)†	0.403
Respiratory rate, /min	24 (20–31)†	28 (24–30)†	0.328
Temperature, °C	37.4 (36.8–39.5)†	37.1 (36.4–38.4)†	0.419
Heart rate, b.p.m.	96 (86–123)†	103 (97–117)†	0.715
Osteoporosis drugs, *n*	1/33	2/19	0.546
Hypertension, *n*	23/33	13/19	1.000
Diabetes, *n*	15/33	43,239	0.240
CVD, *n*	10/33	4/19	0.534
CHF, *n*	15/33	10/19	0.774
Cancer, *n*	9/33	5/19	0.952
CKD, *n*	12/33	3/19	0.203
Alcohol, *n*	11/33	3/19	0.203
Tobacco, *n*	12/33	3/19	0.203
Septic shock, *n*	19/33	8/19	1.000
Vasopressor use, *n*	23/33	8/19	0.078
Ventilator use, *n*	13/33	5/19	0.382
White blood cells, µL	8,390 (2,580–14,120)†	11,600 (8,270–15,115) †	0.185
C-reactive protein test, mg/dL	9.21 (2.72–16.05)†	10.23 (6.06–18.62)†	0.323
Calcium	9.80 (9.40–10.17)†	9.65 (9.37–10.10)†	0.790
pH	7.44 (7.34–7.46)†	7.43 (7.38–7.47)†	0.682
Lac	3.2 (2.1–4.7)†	2.9 (1.9–6.2)†	0.899
Date following CT	9 (3–30)†	8 (4–16)†	0.977
SOFA score	7 (5–9)†	5 (3–6)†	0.056
APACHE II score	25 (14–31)†	24 (21–28)†	0.938
CPC	3 (2–5)†	3 (3–4)†	0.853
Ventilator days	0 (0–6)†	0 (0–1)†	0.319
Vasopressor days	2 (0–5)†	0 (0–2)†	0.054
ICU or HCU stays	5 (3–10)†	5 (4–8)†	0.992
Hospital days	30 (13–60)†	27 (19–57)†	0.575
Barthel index on admission	0 (0–5)†	0 (0–0)†	0.359
Barthel index on discharge	50 (0–100)†	35 (0–67)†	0.224
Fracture after discharge	0/33	2/19	

P values were calculated using Fisher's exact probability test or Mann–Whitney *U*-test.
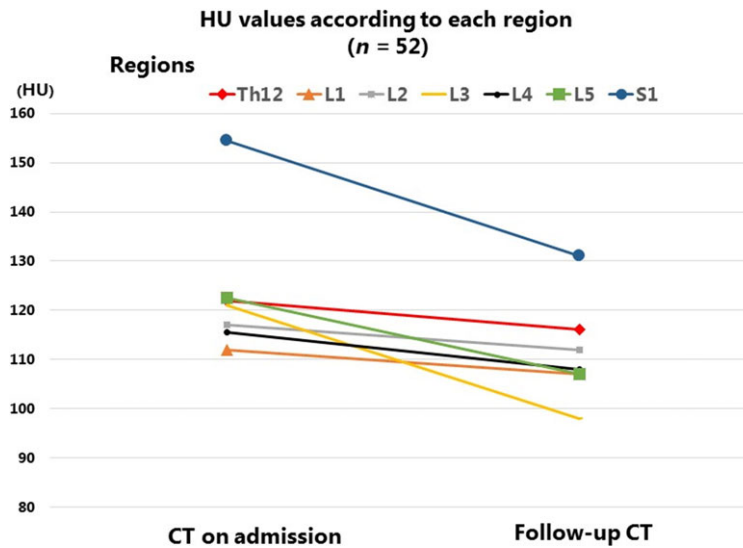†Continuous variables are presented as median and interquartile range values; categorical variables are shown as frequencies or percentages.
APACHE II, APACHE II Acute Physiology and Chronic Health Evaluation II; CHF, congestive heart failure; CKD, chronic kidney disease; CPC, cerebral performance category; CT, computed tomography; CVD, cerebrovascular disease; HCU, high care unit; ICU, intensive care unit; Lac, Lactate; SOFA, Sequential Organ Failure Assessment.

based on HU. This study had two major findings. First, this study showed that BMD significantly decreased after intensive care, especially in the non-osteoporosis groups. This finding is similar to a previous report by Orford *et al.*[3] who found that BMD decreased in the 2 years after critical care. However, it is unknown whe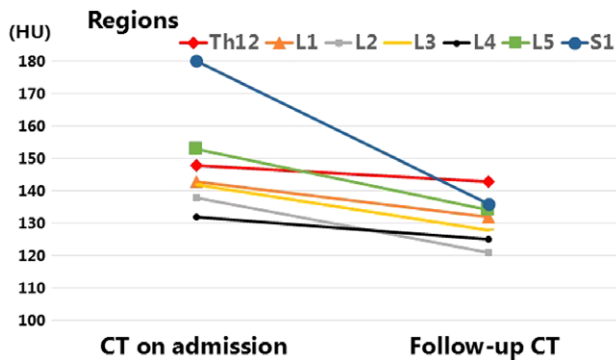ther these differences appeared in the osteoporosis or non-osteoporosis group. Second, the survival rate appeared to be unchanged based on the presence of osteoporosis during the 90-day follow-up.

Osteoporosis is a condition of low BMD and poor bone quality resulting in increased risk of fracture. It represents a major public health issue and warrants clinical screening. In
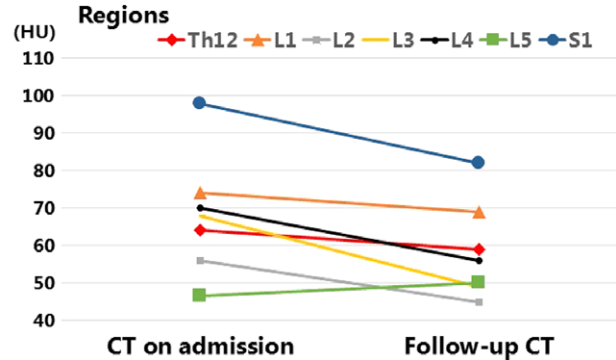
HU values according to each region
(n = 52)

Fig. 3. There were significant vertebral bone Hounsfield units (HU) decreases in patients treated for sepsis at the thoracic (Th) 12 ($P = 0.005$), lumbar (L) 1 ($P = 0.014$), L2 ($P = 0.009$), L3 ($P < 0.001$), L4 ($P < 0.001$), L5 ($P = 0.001$), and sacrum (S) 1 ($P < 0.001$) vertebrae levels ($P < 0.05$) between admission and follow-up computed tomography (CT).
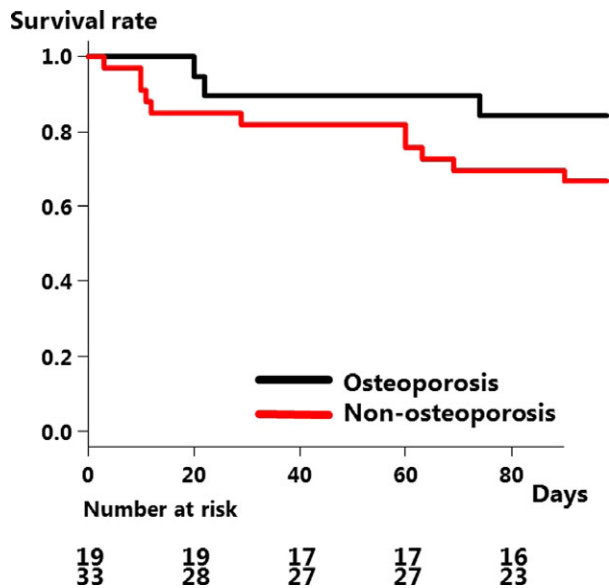

Fig. 4. A, In the non-osteoporosis group of patients treated for sepsis, there were significant Hounsfield units (HU) decreases at the thoracic (Th) 12 ($P < 0.001$), lumbar (L) 1 ($P < 0.001$), L2 ($P < 0.001$), L3 ($P < 0.001$), L4 ($P < 0.001$), L5 ($P < 0.001$), and sacrum (S) 1 ($P < 0.001$) vertebrae levels. B, There was significant HU decrease only at the S1 ($P < 0.001$) level in the osteoporotic group.

the USA, by age 60 years, half of Caucasian women have osteopenia.[10] The current standard of BMD assessment, DXA, is based on a person's BMD T-score at the hip and lumbar spine, according to the World Health Organization diagnostic classification.[6,8,10] Fundamental differences exist between DXA and CT vertebral densitometry. The former produces planar measures obtained in the anteroposterior plane and includes cortical bone, posterior elements, vascular calcification, and degenerative changes, potentially leading to spuriously elevated BMD that does not correlate with

an increase in vertebral body strength, making DXA less sensitive to changes in fracture risk. Helical CT technology produces volumetric measures and allows selective placement of ROIs, which greatly reduce the effect of these confounding factors. Thus, CT provides better accuracy and precision for measuring metabolically active trabecular BMD and monitoring changes over time. Body CT is a common procedure in the emergency department in Japan. Single-level ROI vertebral attenuation measurement at CT is reproducible, requires little effort, and adds no radiation or

Fig. 5. Ninety-day survival curve of the osteoporosis or non-osteoporosis groups of patients treated for sepsis who underwent abdominal computed tomography (CT) to measure change in vertebral bone mineral density. No mortality difference was found between groups. HU, Hounsfield unit.

cost, but can provide valuable BMD data for osteoporosis screening. Many published articles indicate a strong correlation between CT attenuation techniques, HU, and DXA for bone density assessment.[11] Furthermore, emergency physicians often use abdominal CT for diagnosis.

Loss of BMD after critical care has been reported in previous studies.[3] One study showed that patients with acute respiratory distress syndrome had a decreased BMD after 10 days. Orford *et al.*[3] reported reduced BMD in the 2 years after critical care, particularly in women, and stated the efficacy of antifracture therapy to prevent BMD loss in women after critical care. Sepsis results in the systemic inflammatory response syndrome, which stimulates production of inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, interleukin-1, and interleukin-8; these factors stimulate osteoclastogenesis and bone resorption with calcium mobilization into the circulation from bone stores.[4,7] High bone turnover and bone loss, due to negative remodeling balance at the basic multicellular unit, have been described as independent risk factors for fracture.[3,4] Another study reported increased plasma osteopontin in critical illness leading to build-up of the toxic compound cadmium.[12] Cadmium has direct osteotoxic effects on bone tissue, resulting in enhanced bone resorption.[12] In another study, vitamin D deficiency was reported to increase bone resorption.[13] The major circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), and its active form, 1,25-dihydroxyvitamin D

(1,25(OH)$_2$D), were originally recognized as important endocrine hormones in calcium homeostasis and bone health.[13] However, vitamin D deficiency was observed in up to 76% of critically ill patients.[14] Vitamin D supplementation has improved mortality in patients with sepsis.[13,14]

This study has several limitations. First, this was a single-center, retrospective, observational investigation. The number of patients analyzed was small. A multicenter study with a prospective design might be desirable in the future. Second, we did not have data on vitamin D, calcium, or bone resorption or bone formation markers. This study was undertaken at a single medical institution, there were issues with costs, requests for laboratory studies were dependent on the treating physicians, and some physicians did not measure BMD. Additionally, the timing of CT performance was based on the treating physician's preference; ideally, CT would be carried out at the same time for all patients. Finally, we were not able to access medical records concerning bone fractures potentially treated at outside medical institutions. Further research could be needed to determine the efficiency of antifracture treatment in this population, as elderly ICU survivors are at increased risk of fracture; decreased bone strength and bone quality, the hallmark of osteoporosis, lead to an increased risk of fragility fractures and decreased quality of life.

CONCLUSION

IN THIS RETROSPECTIVE analysis, we found that critical care illness, such as sepsis, was associated with reduced BMD loss following critical care. No mortality difference was found between osteoporosis and non-osteoporosis groups.

DISCLOSURE

Approval of research protocol: The study protocol for this research project was approved by the Committee of Okayama Saiseikai General Hospital, and it conforms to the provisions of the Declaration of Helsinki.
Informed consent: Informed consent was obtained from all participants.
Committee of the okayama Saiseikai General Hospital Institutional Review Board. Approval No. 181001
Registration and registration number: Yes.
Animal studies: N/A.
Conflict of interest: None declared.

REFERENCES

1 Fuke R, Hifumi T, Kondo Y *et al.* Early rehabilitation to prevent postintensive care syndrome in patients with critical

illness: a systematic review and meta-analysis. BMJ Open 2018; 8: e019998.

2 Dong Y, Zhao R, Wang C. Tuina for osteoporosis: a systematic review protocol. Medicine 2018; 97: e9974.

3 Orford NR, Bailey M, Bellomo R *et al.* The association of time and medications with changes in bone mineral density in the 2 years after critical illness. Crit. Care 2017; 21: 69.

4 Puthucheary ZA, Sun Y, Zeng K *et al.* Sepsis reduces bone strength before morphologic changes are identifiable. Crit. Care Med. 2017; 45: e1254–61.

5 Mashalkar VN, Suragimath G, Zope SA *et al.* A cross-sectional study to assess and correlate osteoporosis and periodontitis among postmenopausal women: a dual energy X-ray absorptiometry study. J. Midlife Health 2018; 9: 2–7.

6 Hendrickson NR, Pickhardt PJ, Munoz del Rio A *et al.* Bone mineral density t-scores derived from ct attenuation numbers (Hounsfield Units): clinical utility and correlation with dual-energy X-ray absorptiometry. Iowa Orthop. J. 2018; 38: 25–31.

7 Nishida O, Ogura H, Egi M *et al.* The Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). Acute Med. Surg. 2018; 5: 3–89.

8 Demir Ö, Öksüz E, Deniz FE *et al.* Assessing the effects of lumbar posterior stabilization and fusion to vertebral bone density in stabilized and adjacent segments by using Hounsfield unit. J. Spine Surg. 2017; 3: 548–53.

9 Young ES, Reed MJ, Pham TN *et al.* Assessment of osteoporosis in injured older women admitted to a safety-net level one trauma center: a unique opportunity to fulfill an unmet need. Curr. Gerontol. Geriatr. Res. 2017; 2017: 1–6.

10 Watts NB, Bilezikian JP, Camacho PM *et al.* American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocr. Pract. 2010; 16(Suppl 3): 1–37.

11 Pickhardt PJ, Lee LJ, Muñoz del Rio A *et al.* Simultaneous screening for osteoporosis at CT colonography: bone mineral density assessment using MDCT attenuation techniques compared against the DXA reference standard. J. Bone Miner. Res. 2011;26:2194–203.

12 Lee P, Nair P, Eisman JA *et al.* Bone failure in critical illness. Crit. Care 2016; 44: 2270–4.

13 Venkatram S, Chilimuri S, Adrish M *et al.* Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit. Care 2011; 15: R292.

14 Al-Tarrah K, Hewison M, Moiemen N *et al.* Vitamin D status and its influence on outcomes following major burn injury and critical illness. Burns Trauma 2018; 6: 11.