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ORIGINAL RESEARCH

Occurrence of Clinical Bone Fracture Following a Prolonged Stay in Intensive Care Unit: A Retrospective Controlled Study

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Abstract Clinical consequences of critical illness and critical care (CC) on bone health remain largely unexplored. This retrospective study aimed to assess the number of new bone fractures (BF) following a prolonged length of stay (LOS) in intensive care unit (ICU). Adults admitted in our tertiary ICU during 2013 with a stay >7 days were included (CC group). Patients who died in ICU or lost to follow-up were excluded. For each CC patient still alive after 2 years of follow-up, 2 control patients, scheduled for surgery during 2013, were recruited and matched for gender and age. Basal fracture risk before admission was calculated using FRAX tool. General practitioners were phoned to check out new bone fracture (BF) during 2 years after admission. Of the 457 enrolled CC patients, 207 did not meet inclusion criteria and 72 died during FU (median age 72 [65–77] years). New BF occurred in 9 of the 178 patients still alive at the end of FU (5%). Median age of these patients was 64 [53–73] years. Fractured patients did not differ from non-fractured ones based on demographic and clinical characteristics, excepting for FRAX risks that were higher in fractured patients. In the control group, 327 patients were analyzed. Their rate of BF was 3.4% without statistical significance compared to the CC group. FRAX risks were similar in both groups. The risk of new BF in CC group, expressed as an odds ratio, was 50% higher than in the control group without achieving statistical significance (odds ratio 1.53; 95% confidence interval 0.62–3.77; $p = 0.35$). When comparing ICU survivors to patients who underwent uncomplicated surgery in the present preliminary study included limited cohorts, the fracture risk in the 2 years following prolonged ICU stay was not statistically higher. However, CC fractured patients had higher FRAX risks than non-fractured patients. Such screening could help to target prevention and appropriate treatment strategies.

Keywords Critical care · Critical illness · Bone fracture · FRAX index · Long term outcomes

Abbreviations

BF	Bone fracture
BMD	Bone mineral density
BMI	Body mass index
CC	Critical care
CVVH	Continuous venovenous hemofiltration
FU	Follow-up
ICU	Intensive care unit
LOS	Length of stay
PICS	Post-intensive care syndrome

Background

Mortality rates during critical care have significantly decreased then stabilized over the last past years. Surviving critical illness is thus the next challenge: patients discharged from intensive care unit (ICU) have to face significant sequelae that have now been identified by the

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medical community as the post-intensive care syndrome (PICS) [1]. Survivors may suffer from severe and prolonged physical, cognitive, and psychological problems that may lead to serious functional impairments, reduced quality of life and increased health related costs [2]. Among post-intensive care morbidities, ICU acquired weakness is largely described and investigated. However, muscle is not the only part of the locomotion system that may be affected by critical illness and ICU stay. Bone health itself may also be impacted by inflammation, endocrine dysfunction, vitamin D deficiency, immobilization, or corticosteroids use. Nevertheless, clinical consequences of critical illness and critical care on bone health remain largely unexplored.

Several bone turnover markers have been studied in critically ill patients. The measured bone markers varied widely among the studies, as well as methodologies. However, according to a recent systematic review, an increase in bone resorption markers and in immature osteoblast activity seems to be noted, confirming an increased bone turnover [3]. At this point, it is worth noting that caution should be appropriate when dosing bone markers in acute critically ill patients [4]. Pre-analytical conditions may not be met in this particular context (i.e. fasting in case of continuous enteral nutrition), fluid shifts or renal function alteration may interfere with results interpretation. Moreover, matrix effects may be suspected when using immunoassays, due to variations in serum protein concentrations during critical illness [5].

Changes in bone mineral density (BMD) during or after critical care have also been evaluated. Measurements at short and long term after critical illness onset both suggested a decrease in BMD that could led to a potential increased calculated risk of bone fractures [6–8].

In clinical practice, it would be important to know how such biological and physical negative changes influence the occurrence of bone fracture in surviving patients. To the best of our knowledge, only one study investigated the real risk of new bone fracture following ICU stay [9]. That retrospective study recruited ICU patients who required invasive mechanical ventilation for at least 48 h and who survived to ICU discharge. Included patients had in fact a median ICU length of stay (LOS) of 7.8 days. Only women were compared to a healthy matched population. Authors reported an increased fracture risk in older female ICU survivors but bone fracture risk factors previously existing before ICU stay were not taken into account in the analysis.

Knowing the ICU-related factors of altered bone health, long ICU-stayer patients may be expected to be at highest risk of post-ICU bone fracture. At present, it is not clear if bone fractures have to be included in the named "PICS". The present retrospective study aimed to assess the number of new bone fractures following critical illness, focusing on patients with a prolonged ICU stay. In a second phase of the study, a control group was added for comparison. Intent was to compare critically ill patients to surgical patients (and not to healthy people), aiming to highlight a potential impact of critical illness and/or critical care in the occurrence of new bone fracture.

Methods

Population

Critically ill patients were recruited in a 34-bed tertiary adult mixed medical and surgical ICU. All patients admitted during the year 2013 were screened. Adults (>18 years old) with an ICU LOS >7 days were included. Patients who died in ICU and burn patients were excluded. During ICU stay, all critically ill patients benefited from local standard care procedures. Nutrition was administered by oral, enteral, or parenteral route according to patient's status, aiming to obtain daily intakes of 20–25 kcal/kg and 1.2–1.5 g of proteins/kg. Continuous intravenous insulin was administered to maintain blood glucose level between 0.8 and 1.8 g/l. Regional citrate anticoagulation was used in case of continuous venovenous hemofiltration (CVVH) therapy. An early and targeted mobilization strategy was implemented, including passive or active cycling, passive or active range of motion, sitting out of bed, transfers, ambulation, and other mobilization techniques as appropriate.

In the control group were included patients who were scheduled for surgery or invasive procedure during the same year 2013. Patients scheduled for cardiac or cerebral surgery were excluded.

Method

Same method was applied for all patients in both groups, named Critical Care (CC) Group and Control Group. Some data were collected from patients' medical files: demographic data, medical history, and specific data related to ICU stay or scheduled surgery.

For each patient, basal fracture risk before ICU or hospital admission was evaluated using the FRAX tool (Fracture Risk Assessment tool), developed by the University of Sheffield, in association with the World Health Organization. FRAX uses validated clinical risk factors to provide a prediction of individual's risk of fracture in the next 10 years. The risk is expressed in percentages. In the present study, the Belgian version of the FRAX algorithm was used [10, 11], without the measurement of femoral neck bone mineral density (http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9).

During the first semester of 2016, referent general practitioners were contacted by phone for each patient, to check out occurrence of new bone fracture during the 2 years following ICU or hospital admission (in the CC group or Control group respectively). Date and circumstances of fracture were noted, as well as the affected bone. Patients who sustained fractures on multiple occasions were included only for the first fracture. In the present study were considered frailty fractures, defined as fracture occurring spontaneously or after a low energy trauma. Fractures occurring after a high velocity trauma (falls >3 m, motor vehicle related traffic injuries, blunt violence) or pathological fractures were not included.

Calculation of the needed sample size was not achievable due to insufficient available data in the literature, especially regarding the anticipated fracture risk in the control population.

Statistical analysis was performed using Graphpad Prism (version 6.0 for Mac OSX, Graphpad Inc., San Diego, CA, USA). Data were tested for normality using the Shapiro–Wilk test. Results are expressed as medians with interquartile ranges or frequency distribution. Unpaired data were compared using Mann and Whitney test. Proportions were compared using Fisher's exact test. A p value <0.05 was considered to be statistically significant.

Results

Of the 1446 patients admitted in ICU during the year 2013, 457 had an ICU LOS >7 days and were then enrolled. Due to exclusion criteria, 285 patients have been included in the study and 250 were finally analyzed in the CC group (Fig. 1). Of those, 72 died during the follow-up period and were analyzed separately to assess a potential bone fracture as the cause of death. At the end of the 2 years of follow-up, 178 patients were still alive. For each one, two control patients, matched for gender and age, were then recruited among all the patients who attended pre-operative anesthesia consultation in 2013. Less than 10% of these patients were considered lost to follow-up and 327 were finally analyzed in the Control group (Fig. 1).

Descriptive characteristics of critically ill patents and control patients are detailed in Table 1. Control patients did not differ from alive critically ill patients in terms of age, gender, BMI, or basal FRAX risk. Critically ill patients had actually a prolonged stay in ICU and even in hospital.

Among the 72 critically ill patients who died during the 2 years of follow-up, only one patient (a 62 years male) experienced hip fracture 17 months after ICU admission. Yet, his death was not reported to be due directly to this fracture.

Nine alive patients (5%) sustained fracture during the two years after ICU admission. Four of them were men. Fractures occurred after 7.5 (2.4–22.8) months, all in a context of fall at home. All fractured patients experienced only one fracture during the follow-up period. Descriptive characteristics of non-fractured and fractured patients in the CC group are detailed in Table 2. No significant differences were noted between the two groups in term of age, gender, BMI, SAPS II score, ICU length of stay (LOS) or mechanical ventilation duration. None of the fractured patients benefited from a CVVH treatment. Both basal major and hip FRAX risk were significantly higher in the fractured patients when compared to non-fractured patients in the CC group ($p = 0.0029$ and $p = 0.0065$ for major and hip FRAX risk respectively). Major FRAX risks were 16 (5.4–24) % and 5.2 (2.7–8.2) %, and hip FRAX risks were 6.8 (1.4–15.5) % and 1.4 (0.5–3.3) %, in fractured and non-fractured patients, respectively (Fig. 2). Only a few patients received vitamin D supplementation before ICU admission or during ICU stay. Proportion of supplemented patients did not differ between fractured and non-fractured patients. Similarly, corticosteroids treatment during critical illness was not more common in fractured patients when compared to non -fractured patients. Proportion of patients living at home 2 years after critical care admission was statistically similar in the two groups. Even if not different from a statistical point of view, proportion of patients fully autonomous 2 years after ICU admission tended to be higher in the non-fractured group.

In the Control group, 11 patients (3.4%) sustained new bone fracture, 14.5 (6–20.5) months after hospital admission. Each of them was due to a fall. Of note, one of the 11 fractured patients experienced 2 fractures during the 2 years of follow-up: both affected the same bone, the second one occurring more than one year after the initial event. Fractured patients in the Control group were not different from the critically ill fractured patients in terms of age, gender, and BMI. Median age was 63 years in both groups, with IQR 60–83 or 54–69 in CC group or control group, respectively. Female represented 55% of the fractured population in both groups. Fractured patients's BMI was 25.8 (24–29) and 26.7 (22–31) kg/m^2 in CC group and control group, respectively. Basal major and hip FRAX risks were similar in both groups (Fig. 2). Timing of fracture occurrence was not statistically different between both groups.

Proportion of new bone fracture in the CC group and Control group is presented on Fig. 3. The risk of new fracture in the critical care cohort, expressed as an odds ratio, was 50% higher than in the control group without achieving statistical significance (odds ratio 1.53; 95% confidence interval 0.62–3.77; $p = 0.35$).

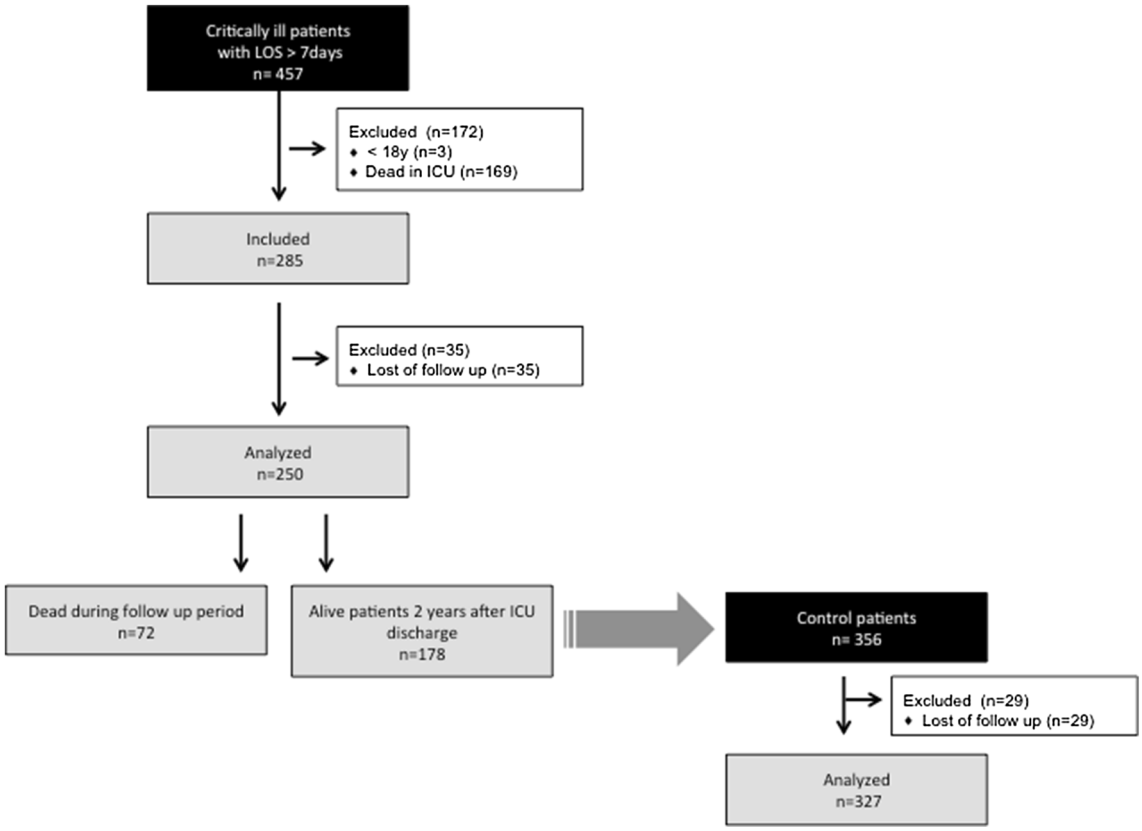

Fig. 1 Flow chart. *y* years, *ICU* intensive care unit, *LOS* length of stay

Discussion

The present study is one of the few interested in clinical bone consequences of critical illness or critical care. The retrospective observations showed that the risk of new bone fracture following ICU admission was not statistically different from that of patients discharged after a scheduled surgery or invasive procedure. These results are similar to those previously published in a retrospective study in which authors demonstrated no significantly higher fracture risk in their entire female ICU cohort followed during a median period of 3.7 years after ICU discharge, when compared to a matched healthy cohort [9]. Compared to that previously published study, the present one brings other insights regarding frailty fracture risk after critical illness. Present analysis was about the global ICU adult population, with no age or sex restriction. Moreover, present results focused on long ICU stayers. Such patients are anticipated to be at higher risk of bone health alteration, as they are also at higher risk of developing ICU acquired weakness [12]. Bone disease may be due to systemic repercussions of critical illness itself, but also critical care including immobilization, treatment strategies, or received medications. There is no consensus in the literature about the definition of a "prolonged ICU stay". It is probably depending on several factors such as hospital type or critical illness type. In the literature, a prolonged ICU stay has been defined as ICU LOS from >4 days up to >14 days according to the studies. In the present study, the usual LOS encountered in our general tertiary ICU (median LOS of 3 days) was used to define what was considered as a prolonged LOS, i.e. >7 days. Such definition has already been admitted as valid in other published studies related to functional outcomes [13]. Finally, follow-up of the included patients lasted two years after admission. Advantage of a limited follow-up period is to link fracture occurrence with the direct consequences of critical care or critical illness, without influence of other future confounding factors affecting bone health.

Both the previously published study [9] and the present one do not completely confirm what was suspected through studies indicating a higher calculated fracture risk based on BMD changes during or after ICU stay. One explanation may be the limited physical capacities that are known to persist from 6 months to 5 years according to studies [2, 14, 15]. Exercises limitations and lower physical functioning may reduce the probability for the patients to find themselves in a suitable situation leading to bone fracture.

Table 1 Demographic, clinical characteristics, and outcomes of included patients in Critical Care group and Control group

	Critical Care group			Control Group ($n = 327$)	
		Deceased ($n = 72$)	Alive ($n = 178$)		
Age, years		72 (65–77)	64 (53–73)		64 (53–73)
Female, *n* (%)		25 (35)	65 (36)		122 (37)
BMI, kg/m^2		26.7 (23–30)	25.2 (23–30)		26.2 (23–29)
Comorbidities					
Cardiovascular, *n* (%)		62 (86)	128 (72)		50 (15)
Respiratory, *n* (%)		27 (37)	52 (29)		39 (12)
Renal, *n* (%)		14 (19)	23 (13)		19 (5.8)
IT DM, *n* (%)		5 (7)	8 (4)		7 (2)
SAPS II		42 (30–54)	44.5 (34–55)		–
Admission category, *n* (%)	Medical	41(57)	76 (43)		–
	Surgical	31 (43)	102 (57)		327 (100)
Admission failure, *n* (%)	Cardiovascular	25 (35)	50 (28)	Abdominal	91 (28)
	Digestive	6 (8)	11 (6)	Endoscopy	5 (1.6)
	Hepatic	2 (3)	5 (3)	Eye	20 (6)
	Metabolic	1 (1)	3 (2)	HPN	2 (0.6)
	Neurologic	8 (11)	32 (18)	Maxilofacial	2 (0.6)
	Other	0	6 (3)	Neurosurgery	34 (10)
	Pulmonary	25 (35)	46 (26)	ENT	45 (14)
	Renal/Urologic	3 (4)	3 (2)	Plastic	23 (7)
	Trauma	2 (3)	22 (12)	Senologic	7 (2.2)
				Urologic	98 (30)
Outcomes					
ICU LOS, days		18 (11–29)	15 (10–23)		–
Hospital LOS, days		42 (29–63)	38 (26–60)		2 (1–4)
Ventilation duration, days		8 (1–17)	7 (1–13)		–
CVVH, *n* (%)		8 (11)	13 (7)		–
CVVH duration, days		5 (2–14)	15 (7–23)		–
FRAX risk					
Major fracture, %		8.5 (6.8–15)	5.4 (2.8–8.5)		5.7 (2.9–10)
Hip fracture, %		3.8 (2.2–6.8)	1.5 (0.5–3.8)		1.5 (0.4–4.1)

Data are showed as median with interquartile ranges or number and percentages

y years, *BMI* body mass index, *SAPS II* Simplified Acute Physiology Score, *IT DM* insulin-treated diabetes mellitus, *ENT* ear, nose and throat surgery, *HPN* hand and peripheral nerve surgery, *ICU* intensive care unit, *LOS* length of stay, *CVVH* continuous venovenous hemofiltration

Notion of basal fracture risk before ICU admission was unfortunately lacking in near all previous studies related to bone health after critical illness. The present study has the strength to have integrated such data in the form of the FRAX risk score. Fracture occurrence after 2 years in the CC group reached or even exceeded the risk predicted by the basal major FRAX score for alive or dead patients, respectively. This highlights the frailty of critically ill patients, comparing to the general population on which the FRAX probability is calculated. Interestingly, critically ill patients who sustained new bone fractures in the two years following ICU admission had higher basal FRAX risks than non-fractured patients. This emphasizes the importance of post-ICU bone fracture prevention, beginning with a screening of patients that should be considered at high risk. Implementation of basal FRAX risk calculation for each patient admitted in ICU could be a first relevant step. However, discriminant value of FRAX risk is not yet known. It is worth noting that FRAX tool calculates a risk of fracture at 10 years. This statement may be of useful consideration when interpreting comparison of basal FRAX risks in fractured and non-fractured patients in both groups of the present study. Similar FRAX risks were observed in the Control group, unlike CC group. This may

Table 2 Demographic and outcomes of non-fractured and fractured patients in the Critical Care group

	Critical Care group ($n = 178$)	
	Non-fractured patients ($n = 169$)	Fractured patients ($n = 9$)
Age, years	64 (53–72)	63 (60–83)
Female, *n* (%)	60 (35.5)	5 (55)
BMI, kg/m^2	25.2 (23–29)	25.8 (24–29)
SAPS II	44 (34–55)	53.5 (28–61)
Outcomes		
ICU LOS, days	16 (10–25)	10 (9–18)
Hospital LOS, days	38 (26–60)	33 (23–80)
Ventilation duration, days	7 (1–13)	2 (0–11)
CVVH, *n* (%)	13 (7.7)	0
CVVH duration, days	15 (7–23)	–
Corticosteroids during ICU stay	28 (16.5)	3 (33)
Vitamin D supplementation		
Before admission	19 (11)	2 (22)
During ICU stay	12 (7)	1 (11)
2 years status		
Living at home, *n* (%)	148 (87.6)	9 (100)
Living in institution, *n* (%)	21 (12.4)	0
Level of autonomy at 2 years		
Fully autonomous, *n* (%)	87 (51)	1 (11)
Needs help, *n* (%)	72 (42.5)	7 (78)
Dependant, *n* (%)	11 (6.5)	1 (11)

Data are showed as median with interquartile ranges or number and percentages

y years, *BMI* body mass index, *SAPS II* Simplified Acute Physiology Score, *ICU* intensive care unit, *LOS* length of stay, *CVVH* continuous venovenous hemofiltration

stress out the role of critical care or critical illness in accelerating occurrence of bone fracture in patients previously at risk.

In the present study, no other association was statistically demonstrated between fracture and ICU characteristics, such as illness severity, CVVH requirement or corticosteroid use during ICU stay. Vitamin D supplementation during ICU stay was quite uncommon in both fractured and non-fractured survivors. Prolonged critically ill patients are at risk of vitamin D deficiency due to reduced synthesis and intakes or abnormal wasting [16]. When considering the Endocrine Society recommendations [17], daily cholecalciferol requirements for adults at risk of vitamin D deficiency range from 1500 to 2000 UI, which is never obtained by the sole nutrition, either oral or artificial nutrition. There is to date no clear evidence that vitamin D supplementation or even treatment is beneficial in term of bone health in critically ill patients. In the VITdAL-ICU study [18], fracture incidence in critically ill survivors with an initial vitamin D deficiency was similar after vitamin D3 supplementation at high dose during 6 months or after placebo. It is unknown if a longer supplementation period would have lead to better bone outcomes, even at a longer term. Moreover, if 30 ng/ml is thought to be the minimal 25OH-D level required for bone health [19], the optimal level and its timing is still not clear. However, these uncertainties should not prevent ICU physician to supply at least at recommend dose in order to reduce an easily avoidable bone weakening.

Some limitations need to be acknowledged. First of all, present results have to be interpreted with caution due to limited included cohorts, making this study potentially underpowered. Preliminary sample size calculation was difficult due to the absence of published relevant data, in particular if considering the risk of new bone fracture in a limited period of 2 years after ICU admission or if considering comparison of critically ill patients with a prolonged LOS to non-healthy and surgical patients. For information purposes, with the same proportion of new bone fractures in each groups, and with a 80% power, more than 3000 patients should have been included a posteriori to get a statistically significant difference between the two groups. Second, two years may be a short follow-up when considering bone health and fracture occurrence. However, this timing avoids interference of later confounding factors other than ICU stay. Third, it is impossible to certify that

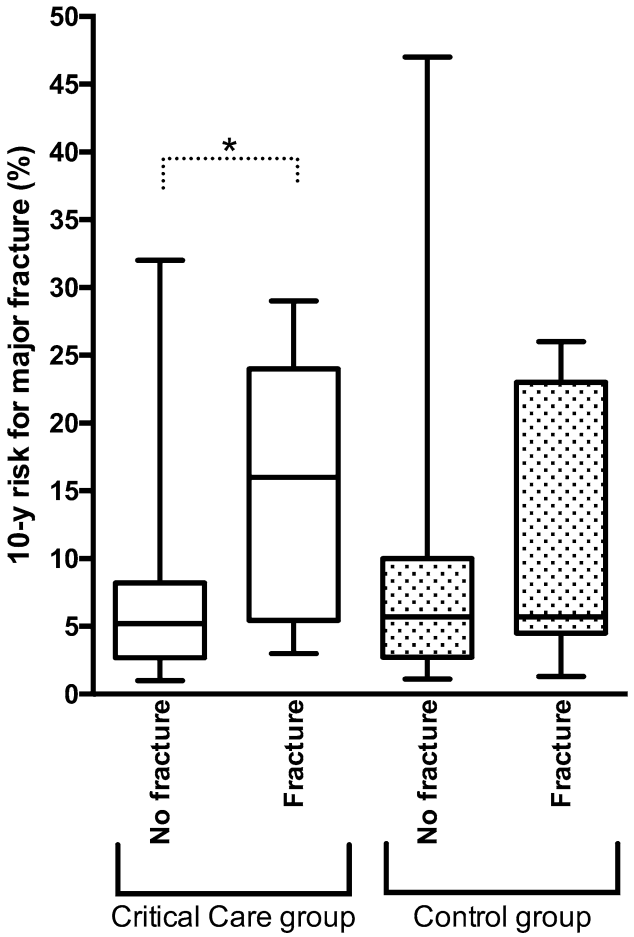

Fig. 2 Major FRAX risk in fractured and non-fractured patients in both groups. *$p < 0.05$

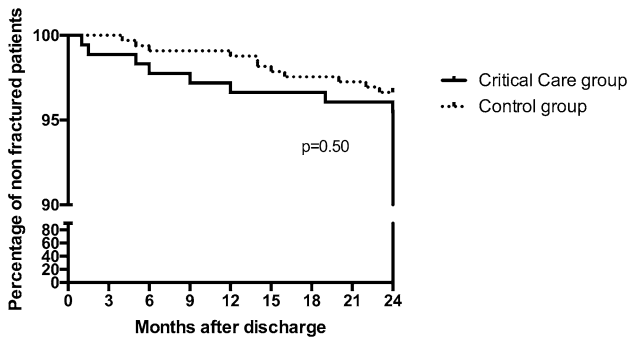

Fig. 3 Kaplan–Meyer curve presenting fracture proportions during the years of follow-up after ICU or hospital discharge in the Critical Care group or Control group, respectively

the contacted general practitioners were aware of all the fractures their patients would have experienced. However, in Belgium, most of the patients have a referent general physician who centralizes all the medical data about his/her patients. This is actually the best way to get information about patient's evolution, as each patient has the choice for both specialists and hospitals (and may thus be followed in different hospital or medical centers). To avoid answers based on memories, physicians were asked to check out occurrence of any new fracture based on the patient's medical chart. Nevertheless, only symptomatic fractures were reported, thus excluding clinically silent fractures (i.e. vertebra fractures) that may have lead to underestimation of fracture occurrence in both groups. Fourth, data regarding bone markers or bone mineral density were not available in the examined medical charts. This could undeniably have added precious information to characterize fractured patients. The lack of consideration about bone health in daily critical care practice has to be admitted, justifying that actually such lab or imaging exams are not routinely requested to explore bone health status in surviving ICU patients. Fifth, due to retrospective method, it was impossible to assess exactly the functional status of included patients. Indeed, it would have been interesting to assess link between muscle performances and fracture incidence. Finally, kidney function was not systematically reassessed during the two years of follow-up, so that it was impossible to evaluate impact of this confounding factor in bone fracture occurrence. Similarly, prescription of drugs affecting bone health, compliance to treatment during the two years of follow-up and their influence on fracture occurrence were not investigated, due to limited availability of such information in a retrospective approach. In particular, data about bisphosphonates prescription should be included in further studies, whether it be a preadmission, an acute care or a post-discharge use. This would help to confirm their beneficial effects on bone density [20] and the potential translation in terms of fracture incidence reduction, as well as on mortality as suggested by recent studies [21, 22].

Conclusions

In this preliminary and retrospective study comparing ICU survivors to patients who underwent uncomplicated surgery (and thus potentially considered frailer that healthy people), and including limited cohorts, clinical evidence of an increased fracture risk after prolonged critical illness is not statistically so obvious. However, the present findings do not entitle to consider bone fractures as a futile outcome after prolonged critical illness. There is a clear and urgent need for further prospective and integrative studies regarding bone health after critical care. This should lead to a better knowledge on the real incidence of new bone fracture in ICU survivors and on which parameters constitute the highest risks. Such approach could be part of what tends to be developed in a growing number of ICU, namely dedicated follow-up clinics for ICU survivors. Meanwhile, based on the demonstrated higher basal FRAX

risk in fractured patients, detecting frail patients should be implemented as soon as ICU hospitalization. Such approach should aim to promote targeted strategies (osteoporosis diagnosis and appropriated treatment) in order to prevent as much as possible the occurrence of new frailty fracture after ICU discharge.

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Author contributions AFR, EC, and OB designed research; AFR conducted research; AFR and OB analyzed data; AFR wrote paper; EC, PD, JYR, and OB critically reviewed paper. All authors approved the final manuscript.

Conflict of interest All authors declare that they have no competing interests.

Ethics Approval The present study was approved by the local Ethics Committee of the University Hospital of Liège (Ref 2015/206).

Informed Consent The local Ethics Committee of the University Hospital of Liège considered that an informed consent was not required, in view of the retrospective method of the study.

References

1. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, Votto J, Harvey MA (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40:502–509
2. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM, Canadian Critical Care Trials G (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304
3. Orford N, Cattigan C, Brennan SL, Kotowicz M, Pasco J, Cooper DJ (2014) The association between critical illness and changes in bone turnover in adults: a systematic review. Osteoporos Int 25:2335–2346
4. Cavalier E, Bergmann P, Bruyere O, Delanaye P, Durnez A, Devogelaer JP, Ferrari SL, Gielen E, Goemaere S, Kaufman JM, Toukap AN, Reginster JY, Rousseau AF, Rozenberg S, Scheen AJ, Body JJ (2016) The role of biochemical of bone turnover markers in osteoporosis and metabolic bone disease: a consensus paper of the Belgian Bone Club. Osteoporos Int 27:2181–2195
5. Rousseau AF, Damas P, Janssens M, Kalin S, Ledoux D, Le Goff C, Gadisseur R, Delanaye P, Cavalier E (2014) Critical care and vitamin D status assessment: what about immunoassays and calculated free 25OH-D? Clin Chim Acta 437:43–47
6. Orford NR, Lane SE, Bailey M, Pasco JA, Cattigan C, Elderkin T, Brennan-Olsen SL, Bellomo R, Cooper DJ, Kotowicz MA (2016) Changes in bone mineral density in the year after critical illness. Am J Respir Crit Care Med 193:736–744
7. Rawal J, McPhail MJ, Ratnayake G, Chan P, Moxham J, Harridge SD, Hart N, Montgomery HE, Puthucheary ZA (2015) A pilot study of change in fracture risk in patients with acute respiratory distress syndrome. Crit Care 19:165
8. Amrein K, Fahrleitner-Pammer A, Dimai HP (2015) Bone—a casualty of ICU survival? Crit Care 19:253
9. Orford NR, Saunders K, Merriman E, Henry M, Pasco J, Stow P, Kotowicz M (2011) Skeletal morbidity among survivors of critical illness. Crit Care Med 39:1295–1300
10. Johansson H, Kanis JA, McCloskey EV, Oden A, Devogelaer JP, Kaufman JM, Neuprez A, Hiligsmann M, Bruyere O, Reginster JY (2011) A FRAX(R) model for the assessment of fracture probability in Belgium. Osteoporos Int 22:453–461
11. Neuprez A, Johansson H, Kanis JA, McCloskey EV, Oden A, Bruyere O, Hiligsmann M, Devogelaer JP, Kaufman JM, Reginster JY (2009) A FRAX model for the assessment of fracture probability in Belgium. Rev Med Liege 64:612–619
12. Griffiths RD, Hall JB (2010) Intensive care unit-acquired weakness. Crit Care Med 38:779–787
13. Patman SM, Dennis D, Hill K (2011) The incidence of falls in intensive care survivors. Aust. Crit. Care 24:167–174
14. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, Himmelfarb CR, Desai SV, Ciesla N, Herridge MS, Pronovost PJ, Needham DM (2014) Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med 42:849–859
15. Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, Horn J, van der Schaaf M (2015) Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Crit Care 19:196
16. Lee P (2011) Vitamin D metabolism and deficiency in critical illness. Best Pract Res Clin Endocrinol Metab 25:769–781
17. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930
18. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic Purkart T, Waltensdorfer A, Munch A, Warnkross H, Stojakovic T, Bisping E, Toller W, Smolle KH, Berghold A, Pieber TR, Dobnig H (2014) Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 312:1520–1530
19. Heaney RP, Holick MF (2011) Why the IOM recommendations for vitamin D are deficient. J Bone Miner Res 26:455–457
20. Via MA, Potenza MV, Hollander J, Liu X, Peng Y, Li J, Sun L, Zaidi M, Mechanick JI (2012) Intravenous ibandronate acutely reduces bone hyperresorption in chronic critical illness. J Intensive Care Med. 27:312–318
21. Lee P, Ng C, Slattery A, Nair P, Eisman JA, Center JR (2016) Preadmission bisphosphonate and mortality in critically ill patients. J Clin Endocrinol Metab 101:1945–1953
22. Schulman RC, Moshier EL, Rho L, Casey MF, Godbold JH, Zaidi M, Mechanick JI (2016) Intravenous pamidronate is associated with reduced mortality in patients with chronic critical illness. Endocr Pract 22:799–808