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ORIGINAL ARTICLE

Sub-optimal serum 25-hydroxyvitamin D level affects 2-year survival after hip fracture surgery

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Abstract

Introduction Hypovitaminosis D is a common condition seen in patients with acute hip fracture. We hypothesize that in addition to the other prognosticating factors, hypovitaminosis D may affect survival in patients treated for hip fractures. The objective of this study is to evaluate the impact of serum level of 25-hydroxyvitamin D (25(OH)D) on the survivability after surgical fixation of hip fractures.

Materials and methods We retrospectively studied data collected from January 2013 through December 2015 at a large tertiary hospital in Singapore. Patient's age, gender, Charlson Comorbidity Index (CCI), delay of surgery, fracture patterns, ASA score, as well as their pre-operative serum levels of 25(OH)D, albumin and calcium were examined. Univariate and multivariate logistic regression were used to analyse post-operative outcomes including short (inpatient, 30 and 90 days) and long-term mortality (2 years).

Results Data from 1004 patients were used. Information on the serum level of 25(OH)D was available in 80% of them ($n = 801$) and more than 90% ($n = 735$) of the patients had a baseline serum level of less than 30 ng/ml. Mortality rate within this group were 1.1% ($n = 9$) at 30 days, 1.9% ($n = 15$) at 90 days and 11.0% ($n = 88$) at 2 years follow up. Hypovitaminosis D was not a significant risk predictor for short-term mortality, but found to be a significant predictor at 2 years.

Conclusions In this study, we showed a high prevalence of hypovitaminosis D among the osteoporotic hip fracture population and its impact on 2-year survivorship after hip fracture surgery.

Keywords Hip fracture · Hypovitaminosis D · Charlson comorbidities index · Mortality · Osteoporotic fracture

Introduction

Hypovitaminosis D is a common condition seen in elderly with acute hip fracture [1–3]. Patients suffering from hypovitaminosis D are at increased risk of osteoporosis [4] and fragility fractures [5]. Its high prevalence has been a global concern, especially in regions such as South Asia and Middle East [6]. Elderly patients with osteoporotic fractures were commonly found to have a much lower serum level of 25-hydroxyvitamin D (25(OH)D) and depending on the country studied, the prevalence could be as high as 91.6% [3, 7–12]. Not only important to musculoskeletal health [13], numerous studies have also positively correlated low serum levels of 25(OH)D with hip fracture at a risk ratio ranging from 1.38 to 1.58 [14–16]. The severity of fragility hip fractures was also found to be significantly worse in patients with hypovitaminosis D [17].

With the projected increase in osteoporotic fractures [18], in particular hip fractures among the aging population [19], it was estimated that compared to the 1960s, there is close to a 3.5 times increase in the number of fragility hip fractures [19]. Its prevalence in United States is expected to reach more than half a million by 2040 [20]. The 1-year mortality risk after sustaining a hip fracture ranges from 10 to 40%, and because of this, there is a growing interest to better understand the predictive factors that could improve the outcomes and survivability after treatment.

Adequate serum level of 25(OH)D is also among some of the key factors in the prophylaxis against a wide spectrum

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of conditions including infectious diseases, autoimmune disorders, diabetes and cardiovascular illness [21]. In a meta-analysis study conducted by Garland et al. a recommendation of more than 30 ng/ml was found to significantly reduce the all-cause mortality caused by hypovitaminosis D [22]. In addition, Saliba et al. also concluded that the risk of death was higher in patients with hypovitaminosis D and those with a serum 25(OH)D concentration of less than 12 ng/ml were twice at risk [23].

There is, however, limited data studying the effects of hypovitaminosis D after hip fracture surgery and its influence on mortality. In this study, we hypothesize that in addition to the other prognosticating factors, hypovitaminosis D may affect survival in patients treated for hip fractures.. The aim of this study is to evaluate the impact of serum 25(OH)D level on the survivability after hip fracture surgery.

Materials and methods

We retrospectively studied data collected from January 2013 through December 2015 at a large tertiary hospital in Singapore. The inclusion criteria were patients of 60 years and above who had undergone surgical fixation or hemi-arthroplasty for traumatic hip fractures to either the neck of the femur or intertrochanteric fractures. Patients with non-osteoporotic fractures and those treated conservatively were excluded. Patient's demographic including age, gender, Charlson Comorbidity Index (CCI), delay of surgery (defined as time to surgery greater than 48 h), fracture patterns, the American Society of Anaesthesiologist (ASA) score, as well as their pre-operative serum levels of 25(OH)D, albumin and calcium were collected and analysed.

Vitamin D status was determined by the serum level of 25-hydroxyvitamin D and categorized into 3 groups based on the Holick Classification [24] as follows: Deficiency, 25(OH)D < 20 ng/ml; Insufficiency, 25(OH)D 21–29 ng/ml; and Normal, 25(OH)D > 30 ng/ml.

All patients were assessed using the age-adjusted Deyo-Charlson Comorbidity Index (D–CCI) [25, 26], calculated based on 17 comorbid conditions, with each assigned a weight of 1 to 6 according to its impact on mortality. The age-adjusted CCI takes into account each decade after 40 years of age as one point. The time to surgery was calculated as the elapsed time from hospital admission to the actual start of surgery.

Albumin level, measured as serum albumin concentration is an important marker for malnutrition, and in this study, hypoalbuminemia was defined as a serum albumin concentration of < 3.5 g/dL. The cut-off for a normal, corrected serum calcium level was set at 2.2 mmol/L.

The post-operative outcomes studied were short-term mortality during inpatient stay, 30 days and 90 days following surgery, and long-term mortality at the 2-year follow-up.

Univariate and multivariate logistic regression analysis were used to assess the effect of variables recorded at baseline on risk of mortality. Variables significant at $p \leq 0.20$ in univariate analysis were entered into a multivariable logistic regression incorporating a forward stepwise selection algorithm with significance levels to enter and stay of 0.05 and 0.10, respectively, the purpose being to identify the dominant risks predictors for mortality after hip fracture surgery. An ROC curve was constructed and significance of change in area under the curve was reported to determine the incremental effect of each additional prognostic factor identified. The association between serum 25(OH)D levels and survivability after hip fracture surgery was further tested using Fisher's exact test.

All analysis were performed using SAS v9.4 software (SAS Inc., Cary, NC, USA). The level of significance was taken as $p < 0.05$.

This study (CRIB Ref: 2015/2134) was approved by the SingHealth Centralised Institutional Review Board, Singapore.

Results

Of the 1087 hip fracture surgeries performed during the period from January 2013 to December 2015, 92.3% ($n = 1004$ patients) met the inclusion criteria and were used in the analysis. Information on the serum levels of 25(OH)D was available in 80% of them ($n = 801$). Defined using the Holick classification and categorized into 3 subgroups, 8.2% ($n = 66$) were normal, 44.3% ($n = 355$) were insufficient and 47.4% ($n = 380$) were deficient.

In this cohort of patient with measured serum 25(OH)D level during admission, the mean ± SD age was 77.7 ± 8.0 years, and 566 (70.7%) were females. There were 482 (60.2%) and 319 (39.8%) femoral neck fractures and trochanteric fractures respectively. The mean time to surgery was 90.7 ± 103 h, and 34.4% ($n = 288$) of surgeries were performed within 48 h. The follow up rate of this study at 2 years was 96.7% ($n = 775$ patients) and 3.3% ($n = 26$ patients) were lost to follow up. The demographics of the study is shown in Table 1.

We saw a mortality rate of 1.1% (n = 9) at 30 days and 1.9% ($n = 15$) at 90 days. At 2 years follow up, 11.0% ($n = 88$) demised, of which, 95% ($n = 84$) had a sub-optimal baseline serum 25(OH)D level (Fig. 1). The serum 25(OH)D level in the mortality group (mean 17.3 ± 6.8) was significantly lower compared to those who survived (mean 20.8 ± 7.2) ($p < 0.05$). The sample size studied in each of the follow up is shown in Fig. 2.

Table 1 Demographics of Study

	N	%
Total number of patients	801	
Mean age, in years	77.7 ± 8.0	
Gender		
Female	566	70.7
Male	235	29.3
Delay in surgery		
Less than 48 h	288	36.0
More than 48 h	513	64.0
Baseline CCI Score		
0–2	63	7.8
3–4	380	47.4
5–6	258	32.2
More than 7	100	12.5
Fracture pattern		
Neck of femur	482	60.2
Trochanteric	319	39.8
Serum 25(OH)D level		
Normal	66	8.2
Insufficiency	355	44.3
Deficiency	380	47.4
Serum albumin level		
Normal	421	52.6
Low	335	41.8
Missing data	45	5.6
Serum calcium level		
Normal	514	64.2
Low	250	31.2
Missing data	37	4.6

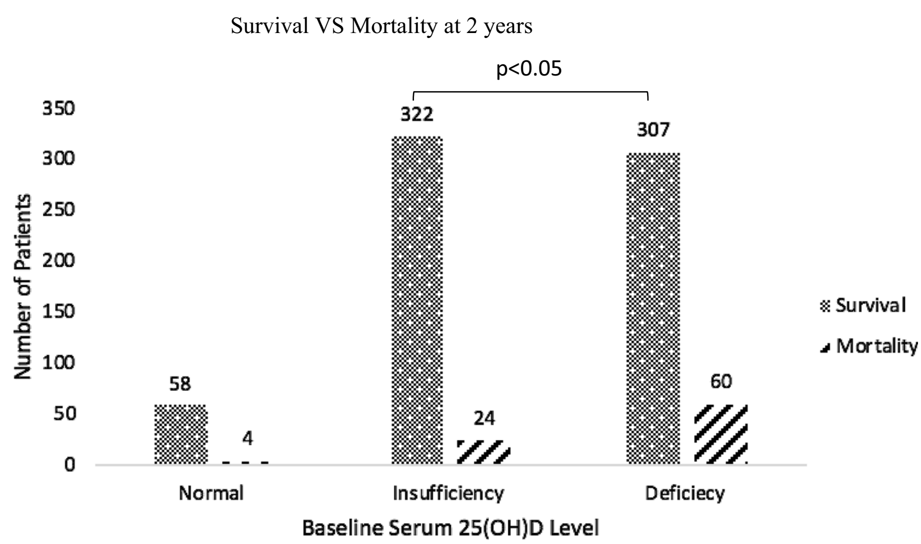
Univariate variate studies showed that hypovitaminosis D was not a significant risk predictor of short-term mortality but a significant predictor for long-term mortality (Table 2).

Using multivariate logistics regression with a forward stepwise selection algorithm, we found that hypovitaminosis D was among the top 3 predictors affecting long-term survivorship after surgical fixation of hip fractures (Tables 3 and 4). The ROC curve constructed was showed in Fig. 3.

Discussion

In this study, we found that more than 90% of the patients had a baseline serum level of 25(OH)D less than 30 ng/ml and this is consistent with other studies conducted locally [27]. We also observed that hypovitaminosis D was a significant risk predictor for long-term mortality at 2 years. The severity of vitamin D deficiency had a significant impact on the survivorship after hip fracture surgeries and patients with a serum 25(OH)D level in the deficiency range were almost twice at risk of mortality (13.2%, $n = 60$) compared to those within the insufficiency range (6.9%, $n = 24$). These results lead us to believe that in addition to affecting all-cause mortality, hypovitaminosis D may be an important risk factor affecting outcomes after hip fracture surgeries.

The study of hypovitaminosis D is a growing field of interest. Traditionally thought to be primarily for the maintenance of bone health and strength, its effect may influence many other aspects of survivorship and serves as an important mediator for the overall well-being and health after hip fracture treatment.



Mortality Ratio	0.069	0.075	0.195
Fisher's exact test	**p < 0.05**		

Fig. 1 Effect of serum 25(OH)D level on mortality after hip fracture surgery at 2 years

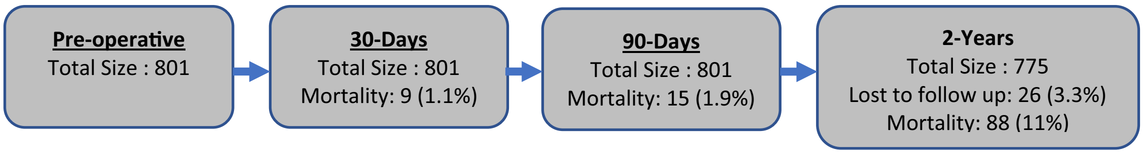


Fig. 2 Flowchart showing sample size with available vitamin D data at each follow up

In a study that evaluated eighty-eight patients with fractures of the proximal femur, Gumieriro et al. found that hypovitaminosis D was not related to an increased risk of mortality within 6 months [28]. Similarly, in another prospective cohort study of 209 patients conducted by Fakler et al. there was no significant correlation between vitamin D deficiency and one year mortality [29]. These results were consistent with our short-term outcomes. However, as new data have emerged showing the association between serum 25(OH)D level and our immune system [30], cardiovascular risks factors including hypertension and diabetes [31–33], renal diseases [34] and its anti-proliferative roles [35] just to name a few, we believe that as an indicator of general health, the impact of hypovitaminosis D may affect survivorship in the longer term.

In a long-term follow up study published by Nurmi Luthje et al. the group found a positive relationship between adequate pre-fracture 25(OH)D serum level and survival after hip fracture surgery [36]. Similarly, we have in our study followed up our patients for up to 2 years after surgery and found that the association between serum 25(OH)D level and risk of mortality after hip fracture surgery became more evident in the longer term. These observations suggest that while the fracture may be adequately treated, inadequate serum 25(OH)D levels may increase the risk of mortality due to all cause effect.

Till date, the association between hypovitaminosis D and hip fracture survivorship remains a debatable topic and the availability of published literature remains scare [28, 29, 36, 37]. Our results have shown that among all the studied risk predictors, hypovitaminosis D emerged as the top three long-term risk factors, making it a high prognosticating indicator during the treatment of osteoporotic hip fractures. As most of the risk factors including gender, age, baseline co-morbidities and fracture types are inevitable, the identification of a modifiable risk factor becomes important in our attempt to reduce the complication rates after hip fracture surgery.

Strengths and limitations

The strength of this study lies in the large cohort study with a high follow up rate of 96.7% at 2 years. We have in our previous published data showed that CCI was the dominant predictor for both short- and long-term mortality [38]. This current study added new insights into the importance of hypovitaminosis D in the peri-operative outcomes after hip fracture surgery and its effect on long-term mortality. There are however several limitations. This is a retrospective study of prospectively collected data and no control group was used in the analysis. Serum level of 25(OH)D on admission reported in this study was based on a single blood test taken prior to the operation and this may not be an accurate long-term indicator of vitamin D deficiency. In addition, no information pertaining to the use of vitamin D supplementation prior to admission was reported in this study. We also did not take into account whether patients who were diagnosed with vitamin D deficiency were started on any treatment after their operation, and hence the short and long-term mortality rates were only correlated with their baseline serum 25(OH)D level prior to surgery.

Future research

The importance of serum 25(OH)D level in patients treated for hip fracture, whether as a surrogate of activity level or health, and the role of vitamin D supplementation for secondary fracture prevention or improved survivorship after hip fractures opens further grounds for research.

Conclusion

In this study, we showed a high prevalence of hypovitaminosis D among the osteoporotic hip fracture population and its impact on 2-year survivorship after surgical fixation of hip fractures.

Table 2 Univariate logistics regression of factors

Inpatient mortality							30-day mortality					
	Frequency		OR	95% CI		*p*	Frequency		OR	95% CI		*p*
	S	M					S	M				
ASA												
1 and 2	714	3	6.21	1.77	21.75	**< 0.05**	710	7	3.16	1.26	7.89	**0.05**
3 and 4	279	8					277	10				
Op delay												
No	342	3	1.28	0.37	4.47	0.702	341	4	1.29	0.48	3.52	0.615
Yes	651	8					646	13				
CCI												
0–2	75	0	1.46	1.21	1.77	**< 0.05**	75	0	1.39	1.18	1.62	**< 0.05**
3–4	453	1					452	2				
5–6	322	3					318	7				
> 7	143	7					141	9				
Gender												
Female	709	6	2.11	0.67	6.63	0.201	705	10	2.03	0.81	5.07	0.130
Male	284	5					282	7				
Age	–	–	1.05	0.98	1.13	0.184	–	–	1.08	1.02	1.15	**< 0.05**
Fracture type												
NOF	592	7	0.89	0.27	2.87	0.839	589	10	0.96	0.38	2.44	0.937
IT	401	4					398	7				
Vitamin D												
Normal	66	0				0.279	66	0				0.229
Insufficiency	354	1	0.6	0.02	14.24		353	2	0.94	0.04	20.21	
Deficiency	374	6	2.31	0.13	42.32		373	7	3.04	0.17	54.33	
Albumin												
Normal	474	5	1.15	0.35	377	0.821	472	7	1.46	0.56	3.85	0.442
Low	413	5					410	8				
Calcium												
Normal	602	6	1.79	0.59	5.62	0.321	598	10	1.38	0.54	3.49	0.503
Low	285	5					283	7				
90-day mortality							2-year mortality					
ASA												
1 and 2	707	10	3.73	1.73	8.04	**< 0.05**	620	68	2.50	1.72	3.65	**< 0.05**
3 and 4	271	16					222	61				
Op delay												
No	340	5	1.76	0.72	4.28	0.213	300	26	2.16	1.38	3.39	**< 0.05**
Yes	638	21					542	103				
CCI												
0–2	75	0	1.43	1.25	1.64	**< 0.05**	68	2	1.44	1.32	1.58	**< 0.05**
3–4	450	4					404	31				
5–6	316	9					268	51				
> 7	137	13					102	45				
Gender												
Female	701	14	2.36	1.11	5.03	**< 0.05**	621	71	2.30	1.57	3.35	**< 0.05**
Male	277	12					221	58				
Age	–	–	1.05	1.00	1.10	**< 0.05**			1.05	1.02	1.07	**< 0.05**

Table 2 (continued)

90-day mortality							2-year mortality					
Fracture type												
NOF	586	13	1.39	0.65	2.95	0.393	515	61	1.75	1.21	2.54	**< 0.05**
IT	392	13					327	68				
Vitamin D												
Normal	66	0				0.304	58	4				**< 0.05**
Insufficiency	350	5	2.09	0.11	38.88		322	24	0.99	0.35	2.82	
Deficiency	370	10	4.13	0.24	72.40		307	60	2.56	0.94	6.99	
Albumin												
Normal	471	8	2.42	1.05	5.55	**< 0.05**	419	44	2.07	1.39	3.09	**< 0.05**
Low	402	16					334	73				
Calcium												
Normal	591	17	1.08	0.49	2.39	0.855	503	87	0.67	0.43	1.05	0.080
Low	281	9					252	29				

OR odd ratio, *CI* confidence interval, *S* survival, *M* mortality

Bold font indicates statistical significance ($P < 0.05$)

Table 3 Multivariable logistics regression analysis of factors affecting mortality after hip fracture surgery

Factors	2 years mortality			
	OR	95% CI		*p* value
ASA score	1.64	0.98	2.72	0.059
Surgical delay	1.94	1.04	3.60	**0.037**
CCI	1.30	1.14	1.49	**< 0.001**
Gender (M vs F)	2.38	1.44	3.93	**< 0.001**
Age	1.02	0.99	1.05	0.298
Fracture pattern	1.56	0.95	2.55	0.080
Serum 25(OH)D Level				**< 0.001**
Insufficiency	1.32	0.41	4.23	0.643
Deficiency	3.45	1.13	10.58	**0.030**
Hypocalcemia	0.58	0.16	2.08	0.991
Hypoalbumenia	1.12	0.68	1.86	0.656

OR odd ratio, *CI* confidence Interval

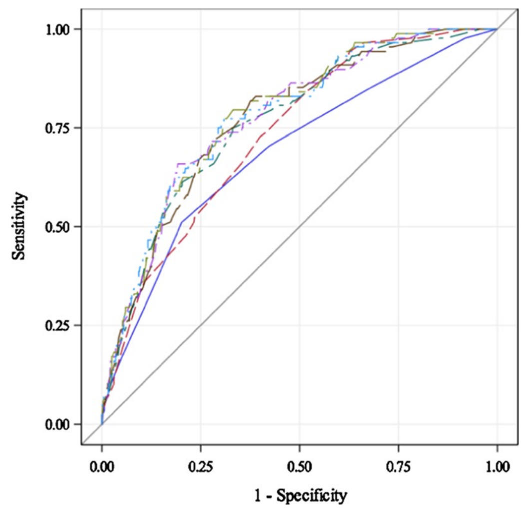
Bold font indicates statistical significance ($P < 0.05$)

Table 4 Multivariable logistic regression analysis incorporating a stepwise selection algorithm (significance levels: enter = 0.05, stay = 0.10) in the analysis of risk factors ($p < 0.20$ in univariate)

2-Year mortality						
Entered	Contributing Factors	OR	95% CI		Wald Chi-squared	*p* value
1	CCI	1.32	1.17	1.50	19.24	< 0.001
2	Serum 25(OH)D Level				14.35	**< 0.001**
	Insufficiency vs Normal	1.25	0.39	3.97	0.15	0.703
	Deficiency vs Normal	3.23	1.07	9.78	4.30	**0.038**
3	Gender	2.41	1.47	3.95	12.23	**< 0.001**
4	ASA	1.70	1.02	2.82	4.16	**0.041**
5	Surgical delay	1.87	1.01	3.47	3.97	**0.046**

OR odd ratio, *CI* confidence Interval

Bold font indicates statistical significance ($P < 0.05$)



Factors	ROC	95% CI		p-value
CCI	0.69	0.629	0.750	-
CCI vs CCI, Vit D	0.73	0.683	0.784	0.053
CCI vs CCI, Vit D, Gender	0.76	0.713	0.815	0.010
CCI vs CCI, Vit D, Gender, ASA	0.77	0.722	0.820	0.007
CCI vs CCI, Vit D, Gender, ASA, Surgical delay	0.78	0.735	0.829	0.002

Fig. 3 ROC Curves for comparison among predictive models at 2 years follow up

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethical approval This study (CRIB Ref: 2015/2134) was approved by the SingHealth Centralised Institutional Review Board, Singapore.

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